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A.M.A. ARCHIVES OF

INTERNAL MEDICINE

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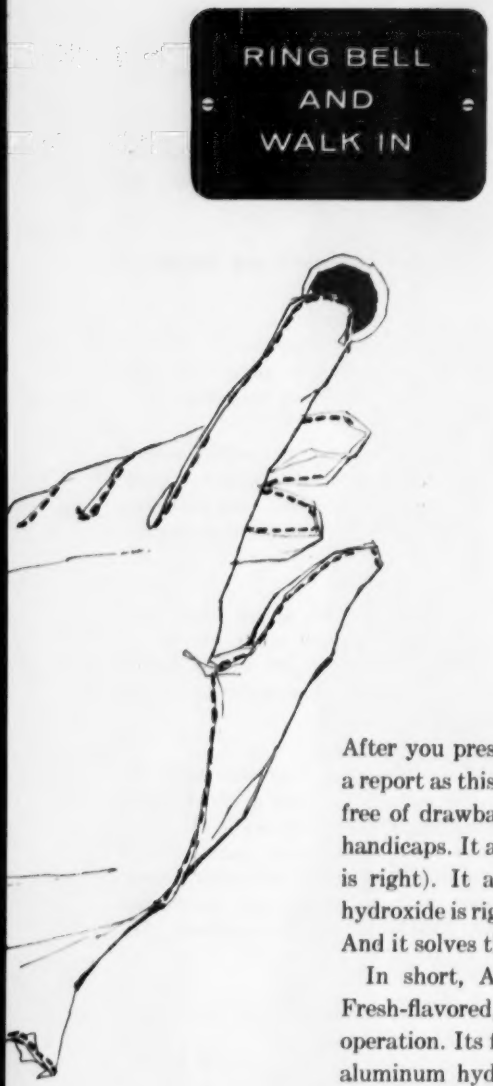

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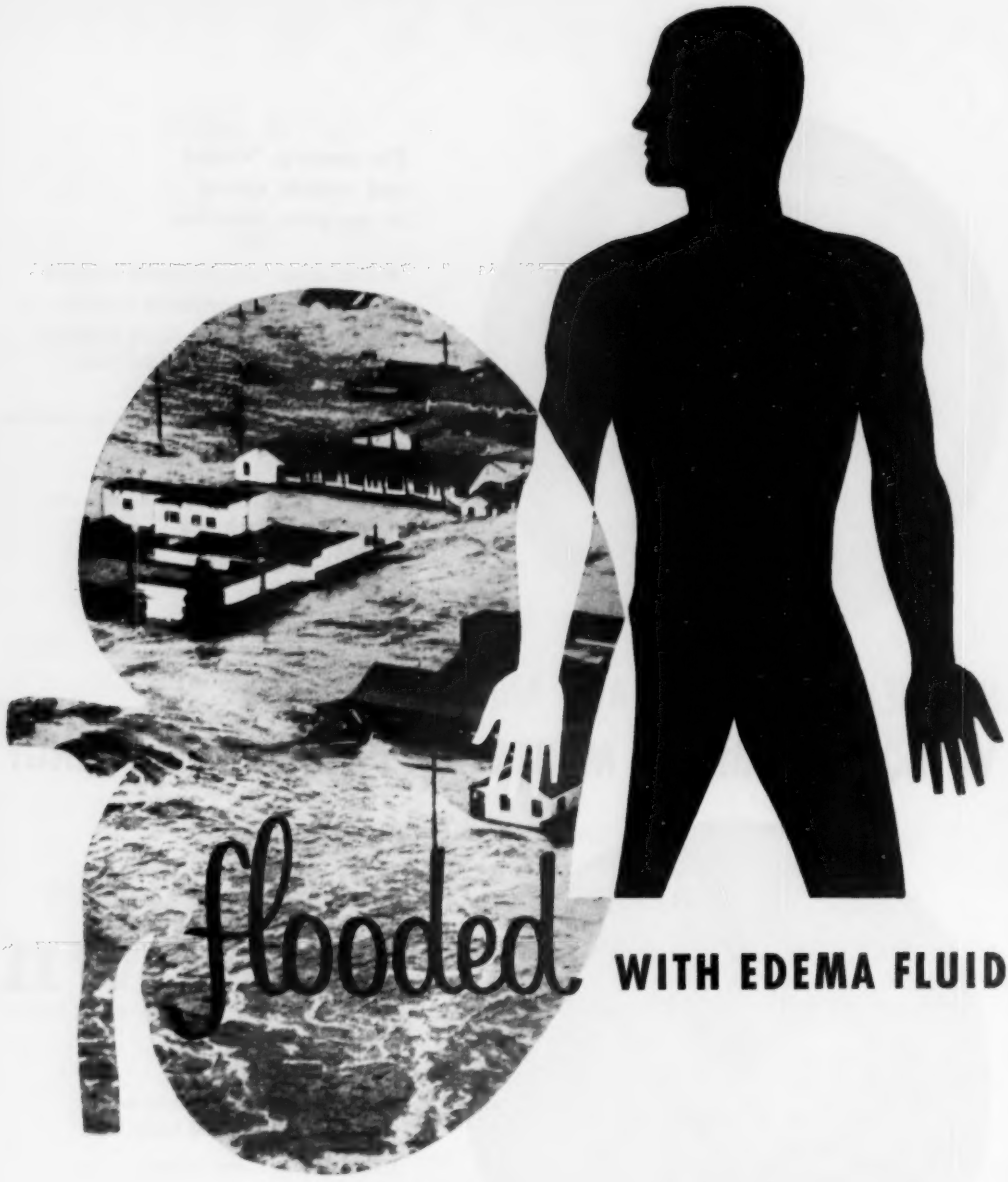

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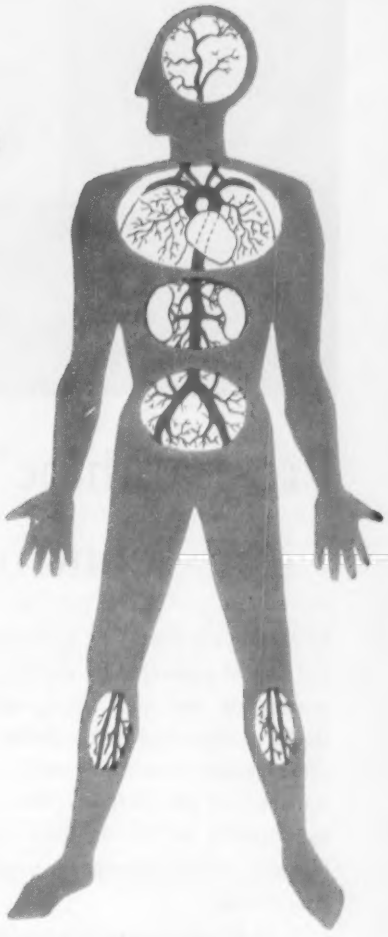

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SEARLE

A.M.A. ARCHIVES OF
INTERNAL MEDICINE

Explaining to the Patient

A Therapeutic Tool and a Professional Obligation

A. CARLTON ERNSTENE, M.D., Cleveland

Standard textbooks of medicine supply excellent articles on recognized diseases, but with rare exceptions the discussions fail to include one feature of paramount importance. No mention is made of the need for explaining to the patient the nature of his problem, the mechanism and significance of his symptoms, and the course the illness may be expected to follow. This omission is unfortunate because, with present-day concentration on pathologic physiology in our medical schools, the subject also receives little or no attention in clinical teaching. As a consequence it may be several years after graduation before a young internist appreciates all that can be accomplished by sufficiently detailed instruction of those under his care. There are two principal reasons why an explanation along the lines indicated is indispensable. In the first place, it is, in many illnesses, a therapeutic tool of basic importance. Secondly, it is one of the best available ways to show personal concern for the patient's welfare and therefore a most effective method for maintaining public support of our free-enterprise system of medicine.

Submitted for publication July 2, 1957.

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Explanation as a Therapeutic Tool

There are many diseases in which the difference between a satisfactory and a poor therapeutic result is determined by the care with which the patient carries out the recommended program of treatment. Attention to details may gain years of comfortable and productive life, and whether or not a person cooperates to the extent required usually depends on whether or not he understands the need for the measures advised. Among the many disorders to which these statements apply are coronary heart disease, congestive heart failure, persistent atrial fibrillation or flutter, pulmonary tuberculosis, emphysema of the lungs, diabetes mellitus, myxedema, gout, and Addisonian pernicious anemia. In psychosomatic problems also, and in much of preventive medicine, proper instruction of the patient is of essential importance. There is not time to discuss the role of explanation in all of these conditions, but I should like to review a few examples.

Angina Pectoris.—There is no statistical evidence that the prognosis of angina pectoris is affected significantly by drug therapy. Treatment, therefore, is directed principally toward protecting the patient from habits, activities, and emotional situations which increase the hazards of the syndrome. In the effort to accomplish this, chief reliance is placed on informing the person as fully as possible concerning his illness. This requires thorough discussion

of the pathogenesis of the symptoms and detailed instruction concerning the mode of action of the various factors which may induce attacks. Reasons should be given for weight reduction in overweight persons, avoidance of overeating, resting after meals, and abstaining from tobacco. The possible aggravating effects of cold weather should be pointed out, and snow shoveling in particular must be prohibited. Emphasis is placed on the importance of avoiding the seizures, but at the same time reasonable assurance is given as to the patient's relative safety so long as he remains free from pain. Mention also should be made of the possibility that with time an effective collateral circulation may develop and bring with it an appreciable improvement in exercise capacity. A talk along these lines places the problem in its true light and often greatly reduces the patient's apprehension. This in turn may result in a considerable diminution in the frequency of the attacks.

Every person who has angina pectoris should be instructed to stop all activities and stand still upon the first appearance of symptoms and to take a tablet of glyceryl trinitrate (nitroglycerin) sublingually if rest alone does not give prompt relief. An occasional patient hesitates to employ this drug either because it causes unpleasant symptoms or because of a mistaken idea that it may have injurious effects. The first of these objections can be forestalled by a brief description of the possible side-effects, with stress on their harmlessness, and the second can be overcome by assurance that the repeated use of the preparation is not detrimental in any way. A reminder should be given, however, that even though glyceryl trinitrate is not harmful a person is not thereby excused from exercising every possible precaution to avoid attacks.

Myocardial Insufficiency and Congestive Heart Failure.—Explanation to the patient also is of primary importance in the treatment of congestive heart failure and other states of impaired myocardial reserve. Regardless of the type of underlying heart disease there must be careful instruction in the nature of the problem and the principles of long-term management if the best possible results are to be obtained. The general concept of myocardial reserve and the significance of dyspnea and other symptoms should be reviewed in understandable terms. One of the commonest reasons for recurrences of cardiac decompensation is failure on the part of the patient to observe the necessary degree of sodium restriction in the diet. A simple discussion of the role of sodium in water retention will usually insure against lapses of this kind. Certain people object to taking digitalis because they erroneously regard it as a heart stimulant employed only late in the course of cardiac disease, and there are others who, contrary to directions, will discontinue its use after having been restored to a state of comfort. These errors can be prevented by a brief description of the effects of the drug on the efficiency of the myocardium and, in atrial fibrillation, on the ventricular rate.

Psychosomatic Disorders.—In persons suffering from nervous tension or anxiety an explanation of the mechanism of the symptoms may result in great improvement even though the underlying source of tension cannot at the moment be identified or corrected. A common problem for general practitioners, internists, and cardiologists is that of sticking or aching precordial pain which has been diagnosed by the patient or by a hurried physician as due to angina pectoris. The exact mechanism of the discomfort is not known, but that it is not evidence of organic heart disease is well established. The pain is not retrosternal in location and does not radiate to that region. At times, however, it spreads upward toward the left shoulder and even down the left arm, usually along the lateral aspect. The sharp, or sticking, variety may be of no more than momentary duration, but the dull or aching type and that which is described as a sense of heaviness frequently lasts for hours at a time. The discomfort is not induced by physical activity but may develop after a period of exertion. Rest and glyceryl trinitrate fail to give prompt

relief. A careful history and physical examination followed by assurance that the pain is arising in the chest wall and is the result of fatigue or emotional tension often results in prompt improvement or complete relief. It is essential that there be a positive explanation of the distress. A statement that there is no heart disease without further elaboration leaves many questions unanswered in the patient's mind and seldom convinces him of the harmlessness of his symptoms. Many persons who have a problem of this kind have the impression that a reliable opinion cannot be given until after roentgenologic and electrocardiographic studies, and it therefore is advisable in the process of explaining the symptoms to mention the lack of need for examinations of this kind. If, after this, one detects evidence of lingering doubt, no matter how slight, an offer should be made to have the studies carried out, but the opinion should be expressed at the same time that the results will be within the limits of normal. The patient then is free to act according to his own wishes, and there can be no cause for dissatisfaction.

Preventive Medicine.—The full potential of preventive medicine can be achieved only if information concerning modern advances in the field reaches the proper persons. For example, means have become available within the past few years for reducing the incidence and severity of rheumatic heart disease. Most initial and recurrent attacks of rheumatic fever can be prevented by early and adequate treatment of streptococcal sore throat, and patients who have rheumatic heart disease or who have had rheumatic fever or chorea can be protected from streptococcal infections and further cardiac damage by the year-round use of sulfadiazine or penicillin. This knowledge will be used to maximum advantage, however, only when all parents, teachers, patients, and physicians have been convincingly informed of its importance.

Many cases of bacterial endocarditis can be prevented by administering appropriate antimicrobial drugs to patients with rheumatic valvular disease or congenital cardiac anomalies before dental extractions, removal of tonsils and adenoids, obstetrical delivery, and operations on the urinary or lower gastrointestinal tract. The benefit of prophylactic treatment will not be realized, however, unless all persons who have cardiac problems of these kinds (or, in the case of infants and children, their parents) are made aware of the presence of the abnormality and of the necessity for preventive therapy.

Explanation as a Professional Obligation

We as physicians have a rightful pride not only in the remarkable advances in medical knowledge during the past forty years but also in the fact that the fruits of these advances have been made available to an ever-increasing proportion of the general population. But we must not become complacent. Although the nonmedical public is fully aware that it is receiving better medical care today than at any time in the past, important areas of dissatisfaction still exist. Proponents of any type of state medicine can be expected to capitalize fully on every deficiency, real or imagined, of the free-enterprise system of practice. It behooves us, therefore, to give careful study to the complaints of the public and introduce corrective measures as promptly as possible.

Perhaps the commonest criticism of the physician of today is a seeming lack of sympathetic interest in his patients. The public is cognizant of the advantages of scientific diagnosis and treatment, but it takes these more and more for granted and desires in addition personal attention comparable to that given by the family doctor of the past. Because there is a desire in each of us to be recognized as an individual, no one enjoys being looked upon solely as an example of a particular disease or syndrome. Furthermore, people come to their doctors because of concern about their symptoms, and their anxiety is seldom allayed unless the physician takes the time to hear the complete story, perform an examination, and then explain the illness and its general prog-

nosis. Emerson once wrote that knowledge is the antidote to fear, and this is just as true in relation to sickness as to other problems in life. The aim of the physician always should be to include in every consultation as much practical information as may be of use to the patient. Instruction of this kind, given unhurriedly and in understandable terms, convincingly indicates true interest and substitutes effectively for much that was included in the personal service of the old-school family doctor. To omit it constitutes not only neglect of a basic obligation to the patient but also failure to do one's part toward correcting a major cause of discontent with present-day medical practice.

I am not laboring under the illusion that the family physician of thirty or fifty years ago won his place in the esteem of his patients because he explained everything to them. As a matter of fact, explanation appears to have been just as much an undeveloped art then as now. This, however, was largely unavoidable because of much greater gaps in medical knowledge at that time. The physician, as a consequence, often was forced to substitute an air of assurance and a skillful bedside manner for lack of precise information. The successful practitioner combined these with the best available measures of treatment and an understanding concern for the patient, and the combination was rewarded by the respect and love of his community. Times change. The public is better informed on medical affairs today than at any time in the past and is kept well abreast of scientific advances by the press. It expects the physician to keep himself equally well informed and promptly transmit the benefits of all discoveries to those who consult him. A self-assured attitude no longer protects from searching interrogation, and the conscientious doctor of today will encourage enquiries and answer them patiently. Certain people fail to ask questions because of timidity, fear of appearing ignorant, or apprehension about the answers. With experience an observant clinician acquires increasing insight into human nature and becomes intuitively aware of what the person under his care would like to know. If he will take the time to cover this information in a more or less incidental manner in his summary and then invite further discussion he can hardly fail to win the appreciation and confidence of the patient.

One of the greatest tests of a physician's skill in explanation is encountered in patients who have cancer, for there are few problems so fraught with misconceptions on the part of the afflicted person and his family. I believe one should base his course on the premise that most people appreciate knowing the truth and most are better off for knowing it. The opinion is held in certain circles that the term cancer should never be employed in talking with the patient, but this seems to me to be doubtful wisdom because, among other considerations, indefiniteness may lead to serious procrastination. Almost always the wisest policy is to present the story as accurately as one can but with as much tempering reassurance as the situation justifies. If the lesion is one which offers a prospect of long-term surgical cure, such as carcinoma in situ of the cervix or early carcinoma of the sigmoid colon, the patient's morale can be bolstered by a short discussion of the differences in behavior of neoplasms arising in different tissues or organs. Even when the outlook is more grave, fear can be minimized and hope sustained by implications which are not in any sense misleading. For instance, a person can be told before operation that he must agree to return for follow-up examination at intervals of three months for the first two years, then every six months for the next three years, and after that once a year. The inference is clear and cannot fail to be a source of encouragement. Indirect support of this type is justifiable, however, only when the physician honestly believes that there is a reasonable chance that the patient will live for the period specifically outlined.

A policy of sympathetic frankness also is best in dealing with persons who have inoperable cancer. Evasiveness on the part of the physician is liable to be interpreted as

evidence of uncertainty or unconcern or as implying a future holding terrors too horrible to contemplate. Deterioration of morale inevitably follows, and this often results in recourse to quacks. Straightforward but kindly discussion, on the other hand, helps the patient accept a situation that cannot be changed and aids him in making the most of the time that remains to him. Reasons must always be given for not advising an attempt at surgical removal of the growth. Certain persons may adopt the attitude that death after an operation is preferable to living with a cancer, and this should be corrected by pointing out that many persons live comfortably and at times for relatively long periods in spite of the presence of incurable malignant disease. Fear of pain is uppermost in the minds of many. Assurance must be given that most cancers do not cause great discomfort and that reliable measures for its control are available if it should occur. There also are patients who become fearful that because no cure is in prospect the physician will dismiss them to the care of the family or some less busy colleague. It should be made clear from the beginning, therefore, that one fully intends to maintain his interest, see the person at regular and not too infrequent intervals, and continue to be of every possible assistance. The friends and relatives of patients who have been treated in this manner will not be hard to convince that similar care cannot be expected under any system of government-sponsored medicine.

This discussion has stressed the importance of explanation to the patient, but I should like to point out before closing that there is often an equal need for instructing the members of the patient's family. There are patients who at first are unwilling to submit to the degree of self-discipline necessary to secure the optimum response to treatment, and in situations of this kind the persuasion of a well-informed family may be of great help. Of equal importance is the fact that a clear explanation of the problem may spare the patient the well-intentioned annoyances of overly protective relatives. Furthermore, family members who do not understand the nature of an illness are more likely to become dissatisfied, and this in turn may lead to criticism of the entire medical profession. A few minutes spent in explaining the patient's problem to those closest to him seldom fails to secure the cooperation and gratitude of the entire family.

In a memorable address some thirty years ago, my beloved chief at the Thorndike Memorial Laboratory, Francis W. Peabody, remarked, "The good physician knows his patients through and through, and his knowledge is bought dearly. Time, sympathy and understanding must be lavishly dispensed, but the reward is to be found in that personal bond which forms the greatest satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient."[1] Let us not forget these words of one who understood.

Summary

An explanation to the patient concerning the nature of his illness, the rationale of its management, and the general prognosis is an essential part of the practice of medicine. Not only is it the most effective way to secure cooperation in carrying out treatment, but it is also one of the most convincing ways of manifesting personal interest in the patient comparable to that given by the family doctor of the past. If one neglects it he runs the risk in many conditions of falling far short of the best possible response to therapy and also fails to do his part in combating the too common criticism that the physician of today's free-enterprise system is lacking in sympathetic concern for those under his care.

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Pathogenesis of Renal Infection

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The pathogenesis of renal infection has no uniform pattern, but infection is the result of one or usually several different factors. Clinical and experimental observations show that an anatomically and functionally normal kidney is quite resistant to infection, and, on the other hand, all kidneys are very vulnerable to infection under certain circumstances. We have found that up to 10% of persons examined by consecutive autopsies had pyelonephritis,[1] and in clinical studies 15% of patients with hypertension,[2] 58% of those who had a nephrectomy because of unilateral kidney disease,[3] and 70% of patients with chronic urinary tract infections were found to have pyelonephritis in a biopsy specimen.[4] Among these patients the clinical illness and mechanisms of pathogenesis varied greatly.

Concepts of Pathogenesis of Renal Infection

Much time and discussion have concerned the route by which bacteria lodge in the kidney. Recently Beeson has reviewed the evidence in this controversy.[5] In the epidemiology of renal infection among different groups of patients the route of infection is a most important factor, but the interstitial nephritis which results is quite similar histologically, regardless of the medium through which the bacteria enter.[6] Through the various routes, experience shows that bacteria frequently reach the kidney. The subsequent course of the infection is determined by the properties of the bacteria, the characteristics of the kidney, and the modification of their interrelationships by certain host factors. In figure 1 a classification of these interrelationships is presented under five general categories. At the one extreme is the specific nephropathogenicity of particular bacterial strains, and at the other is the specificity of the host, with all of the individual factors that are peculiar to him. The interrelationships also are modified by three other determinants. They are (1) genetic factors which predispose to infection, owing to congenital abnormalities of the kidney, (2) acquired structural alterations of the genitourinary tract, and (3) certain functions of the kidney as an excretory organ of the host which encourage infection.

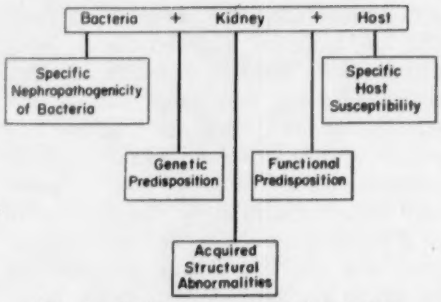

Fig. 1.—Pathogenesis of renal infection.

Specific Nephropathogenicity of Bacteria

The kidney does not filter bacteria to any greater extent than some other organs; but

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bacteria that become sequestered there proliferate rapidly, and some species may persist for long periods of time.[7,8] Our knowledge regarding the specific nephrotoxicity among different bacterial genera is scanty. Some general considerations are species properties, virulence, and survival in kidney. Mixed cultures are common, especially among patients with gross anatomical abnormalities of the genitourinary tract. In our studies 68% of mixed urine cultures came from this group of patients, whereas only 21% of infections with a single species were from patients with anatomical abnormalities.[9] The relative importance of symbiosis in the pathogenesis of the renal infection, however, is unknown.

In nearly all types of infection strains of high and low virulence and often nonpathogenic strains are known. An example with regard to genitourinary disease is Corynebacterium renale, a diphtheroid bacillus, generally considered nonpathogenic but which causes pyelonephritis among cattle and mice.[10,11] Braude and co-workers[12] observed that the virulence of strains used in the production of experimental pyelonephritis in rats declined rapidly upon serial cultivation in broth after their isolation from the urine of patients. Other workers have been unable to increase virulence appreciably by culturing bacteria in kidney tissue.[13] Aside from virulence per se, "urea splitting" and motility, among other bacterial properties, are believed to influence the nature and course of renal infection.[14]

Gram-negative bacilli usually cause acute pyelonephritis and also acute exacerbations among persons with chronic urinary infection. Patients with chronic pyelonephritis, however, frequently do not have acute symptoms.[4,15,16] From such patients more than one-half of the bacterial isolates from kidney biopsy specimens were Gram-positive strains, which were also present in the urine, usually in mixed cultures, and generally considered nonpathogenic.

Staphylococci and enterococci were observed to persist longer in the kidneys of infected rats than Gram-negative bacilli, which produced more acute inflammation and faster resolution.[7] Thus Gram-positive bacteria might be quite important in the pathogenesis of chronic pyelonephritis, although Gram-negative strains usually cause acute pyelonephritis.

Genetic Predisposition to Infection of the Kidney

The frequent occurrence of renal infections among persons with gross congenital abnormalities of the genitourinary tract is common knowledge. Recently certain microscopic congenital abnormalities have been reported, of which some and perhaps all are of importance in the development of renal infections. The disorders can be either congenital or hereditary (Table 1).

By microdissection of the kidney pyelonephritis in the newborn has been ascribed to a congenital immaturity of the nephrons.[17] In a similar manner microscopic dysplasia has been suggested as a primary cause of focal scars on the surface of the kidneys among adults.[18] The dysplastic tissue is extremely susceptible to infection, which is often interpreted as the cause of the scars. These observations are of great importance and deserve further investigation. If the concepts are correct they might explain the focal nature of pyelonephritis in some patients, whereas the majority of those with chronic urinary infection have diffuse involvement of the kidney.[4] Data regarding infections associated with other microscopic abnormalities of the nephrons, such as the one found in the Fanconi syndrome, would be of interest, but sufficient observations are not available.

TABLE 1.—*Genetic Predisposition to Kidney Infection*

I.	Congenital
	Dysplasia or immaturity of nephrons
	Calyceal sinus backflow
	Abnormal collecting system
	Aberrant vessels
II.	Hereditary (familial)
	Cystic or horseshoe kidney
	Hereditary interstitial pyelonephritis

Linneweh [19] found urinary tract infections during the first year of life as common as in all children from ages 1 to 14. On the basis of the frequency of occurrence in different sexes he concluded that descending infection was commoner in infancy than later life. Therefore the high incidence of pyelonephritis often ascribed to diaper soiling might be a reflection of early susceptibility to renal infection among babies with microscopic immaturity or dysplasia of the nephrons. Also of interest with regard to congenital abnormalities is the observation of a 12% incidence of urinary tract infection among infants with congenital syphilis.

Backflow into the calyceal sinuses and pyelotubular backflow are other conditions that might participate in the pathogenesis of renal infection. Köhler [20] found that from 4% to 25% of persons showed backflow of dye injected for routine retrograde pyelograms. This did not require increased pressure, whereas among other patients no backflow occurred even with high pressure within the renal pelvis. The findings, which were believed to be a characteristic of the kidney structure and not caused by calyceal rupture, are obvious routes for the extention of infection.

Among the familial conditions attention has been drawn within the last few years to a syndrome called hereditary interstitial pyelonephritis. Among the kindreds reported [21-23] renal disease resembling chronic pyelonephritis which progressed to uremia and death among males was an incompletely sex-linked dominant trait. Susceptibility to bacterial pyelonephritis was great among these kindreds, but the epidemiology and several clinical features of the syndrome as well as certain histologic findings distinguished it as another example of a congenital renal abnormality in which infection contributes to the pyelonephritis and renal failure but in which it is only secondarily and partly responsible. More than one-half of the patients with evidence of renal disease had negative urine cultures even though pyuria was present. Kindreds with horseshoe or cystic diseases of the kidney in which the congenital abnormality is grossly apparent are similarly vulnerable to bacterial infections of the kidneys.

Finally, while no firm data are available, the frequency with which patients with chronic urinary infection relate information about kidney disease among their relatives suggests more than coincidence.

Acquired Structural Predisposition to Renal Infection

The literature is abundant with examples of the increased susceptibility to infection of the urinary tract after structural abnormalities are acquired. Some of these are listed in Table 2. One of the commonest is obstruction of the urinary passages. Experimental ligation of the ureter in animals, when followed by infectious challenge that is innocuous if the kidney has a free urinary passageway, produces severe pyelonephritis.[24]

Among patients MacDonald and his coworkers [25] found prostatic hypertrophy in one-half of the male patients who had significant bacteriuria at the time of autopsy. Among females the mechanical alterations produced by a gravid uterus are at least in part responsible for the increased occurrence of pyelonephritis among pregnant women.[26] In a study of patients with unilateral hydronephrosis we found that 58% of them had pyelonephritis.[3]

Acquired structural changes in the renal parenchyma per se also might be factors in the pathogenesis of kidney infection. De Navesquez [27] has demonstrated the importance of scars from healed pyelonephritis.

TABLE 2—*Acquired Structural Abnormalities*

I.	Intrinsic urinary disorders
	Obstruction of urinary passages
	Hydronephrosis
	Healed infection (scars)
II.	Biochemically induced lesions
	Nephrocalcinosis
	Hormonal responses
	Potassium deficiency
	Nutritional deficiency
III.	Extrinsic alterations
	Catheterization
	Foreign bodies (instruments)
	Trauma

In experiments with rabbits Gram-negative bacteria which failed to produce any lesions in normal rabbits induced a fatal pyelonephritis among animals that had recovered from kidney infection produced by staphylococci. In another type of experiment Beeson [8] has produced focal lesions in the kidney by means of an electrocautery needle. Such scars located in the cortex failed to increase susceptibility to pyelonephritis from bacteremia. Similar lesions placed in the medulla caused a wedge of pyelonephritis that extended peripherally to the cortex. In the pathogenesis of this lesion rapid multiplication of bacteria in the damaged site was important rather than the accumulation of more bacteria from the circulation.

Histologic alterations of the kidney can be induced biochemically. Nephrocalcinosis from hypervitaminosis D or associated with sarcoidosis may be such examples. Progesterone, whether from pregnancy or medication, induces hypertrophy and dilatation of the renal pelvis and upper ureter.[28] Estrogen has produced different morphologic changes in the kidneys of hamsters.[29] Recently potassium deficiency has been observed to cause microscopic changes in the cells of the tubules and in the renal papillae.[30,31] Pyelonephritis has been a common clinical finding among patients with potassium deficiency.[32] Other nutritional deficiencies, such as choline or cyanocobalamin (vitamin B_{12}), which, in gravid rats, produced a high incidence of renal lesions among the offspring, is another biochemical mechanism for histologic changes in the kidney.[33] Data are scanty regarding the importance of such lesions in the pathogenesis of pyelonephritis, but there is reason to believe they can predispose the organ to infection in a fashion similar to renal scars and other microscopic abnormalities.

Catheterization.—Among the acquired abnormalities listed as extrinsic in origin catheterization stands paramount as a means of initiating urinary infection among susceptible persons. The lack of sterility of the urethra in both male and female as compared with the bladder urine has recently been studied.[34] The entry of micro-organisms from the urethra or external genitalia into the bladder urine among patients with an inlying catheter usually requires less than 48 hours.[35,36] The clinical importance of this route in establishing and transmitting infections with antibiotic-resistant bacteria has been recognized.[37,38]

Because catheterization is often necessary and may contribute so much to the study and treatment of patients with urinary infections we have studied the role of intermittent catheterizations in the pathogenesis of pyelonephritis. Fifty-eight patients attending the outpatient clinic because of hypertension have been catheterized 169 times at intervals of two to four weeks. None of the patients received any antibacterial treatment during the period of study. Quantitative and determinative bacteriologic cultures were done on each specimen collected. The results are shown in Figure 2 and Table 3. Previous studies have shown that the level of significant bacteriuria as determined in our laboratory was 100,000 or more micro-organisms per milliliter of urine.[39] In the present study, if one ex-

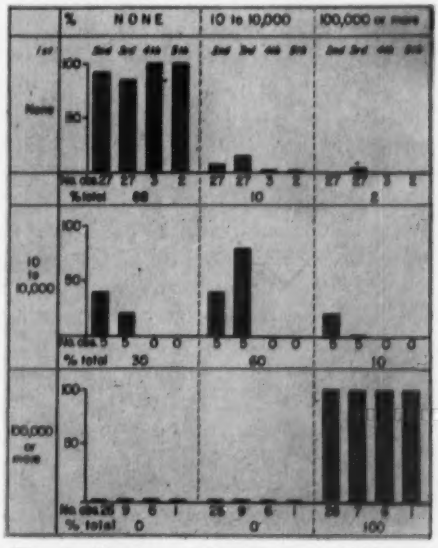

Fig. 2.—Number of bacteria per milliliter of urine in successive catheter specimens.

TABLE 3.—*Frequency of Change in the Species of Bacteria After Catheterization*

Consecutive Catheter Specimens of Urine				Times Species Changed, No.	Pairs Observed, Total	Change in Species, %
First Culture	Bacteria/Ml.	Second Culture	Bacteria/Ml.			
Neg.	0	Pos.	10–10,000	4	58	7
Pos.	10–10,000	Pos.	10–10,000	3	5	60
Pos.	10–10,000	Pos.	100,000	2	2	100
Pos.	100,000	Pos.	100,000 *	13	42	31
Potentially induced infection				22	107	21
Pos.	10–10,000	Neg.	0	3	10	30
Pos.	100,000	Pos.	10–10,000	1	1	100
Pos.	100,000	Pos.	100,000 †	8	42	19
Spontaneous variation				12	53	23

* A new or additional species in a mixed culture.
† A decrease in the number of species in a mixed culture.

cluded this group of patients, sterile urine was obtained from 27 of 32 patients, or 82%. Among the group of 27 that had no growth in the initial specimen 25 also had sterile urine in the second specimen; 23, in three successive specimens, and all samples, from 3 patients catheterized four times each and from 2 catheterized five times. Thus, 88% of 59 subsequent observations among the group that had neither infection nor contamination of the first specimen were consistently sterile specimens. Ten per cent of the subsequent specimens had 10 to 10,000 organisms per milliliter of urine. Only one patient, or 2% of the observations after initial catheterization, showed a significant bacteriuria.

Among five patients whose initial urine specimens contained 1 to 10,000 bacteria per milliliter, 60% of the subsequent 10 observations were the same, while 30% became sterile and one specimen, or 10%, contained more than 100,000 organisms per milliliter. Hence, this group of patients without significant bacteriuria nevertheless was quite consistently distinct from the group of patients with sterile urine. Patients whose initial urine specimen was infected with 100,000 or more organisms per milliliter showed the same result in all of 42 subsequent cultures, which again verified them as a distinct group with true bacteriuria.

By the criterion of quantitative bacteriuria the maximum rate of infection induced by repeated intermittent catheterization in the outpatient clinic was 3%. In a study of women in the hospital Marple found 4% clinical infections after catheterization.[40]

The possibility of the introduction of new bacterial species into the urine is equally as dangerous as the initiation of infection. The results of 119 pairs of successive catheter specimens were analyzed for changes in the bacterial species recovered from the urine. The results are given in Table 3. Changes in the species were common when a low degree of bacteriuria was observed in one or both specimens. In all of the few observations where the number of bacteria increased or decreased significantly the bacterial species also changed. Among the group with more than 100,000 organisms per milliliter in both specimens, 31% of the second specimens of the pairs contained a new or additional species of bacteria.

In the lower part of Table 3 are shown findings on 12 pairs of consecutive catheter specimens in which there was a decrease in the number of bacterial species present in the urine obtained from the second catheterization. These constitute 23% of the pairs in which such a change might have been observed.

The total potential introduction of new infection by the criterion of change of species was 21%; the observed spontaneous variation among species in the urine was 22%. From these data intermittent catheterization of patients in our outpatient department does not appear to be a significant factor in the pathogenesis of pyelonephritis.

Functional Predisposition to Kidney Infection

Certain functional demands placed on the kidney influence the ease or difficulty with which urinary tract infections and subse-

quent pyelonephritis develops. Some of these are as follows: urine concentration and acidity, metabolic status (glycosuria), excretion of certain drugs, hemodynamics, and urine flow and reflux. The outstanding example is glycosuria caused by diabetes mellitus.[41,42] The composition of the diet may exert an effect in either direction. Thus, considerable work on treatment of infection with ketogenic diets preceded the antimicrobial drugs, and β-hydroxybutyric acid in the urine was found to have considerable bactericidal activity.[43] Certain drugs which are excreted in the urine have been observed to produce pyelonephritis frequently among the recipients. One of these is Dapsone (4,4′-diaminodiphenyl sulfone).[44] Some workers believe certain of the antibiotics predispose the person to urinary infection, and other medicines also are under suspicion.[45]

One mechanism by which infection might be encouraged is the excretion of urine that is a better medium for bacterial growth. A test of this hypothesis has been made by observing the ability of bacteria to grow in urine from normal persons and in a pool of urine specimens from 22 persons with urinary infections. The results were compared with the growth obtained in a balanced salt solution and in enriched bacteriologic medium. Each pool of urine was filtered and divided into aliquots. Each aliquot was altered by adding a different concentration of some constituent that might be in the urine and inoculated with a seed culture of Escherichia coli or enterococci. The results are shown in Figure 3.

At a pH 6.0 Hank's balanced salt solution supported 29% of the maximal growth obtained in the bacteriologic medium. Urine from normal persons allowed 36% maximal growth, and that from persons with urinary infections, 39%. When the pH was adjusted to approximately 4.5 there was little effect upon the growth in salt solution but a substantial reduction of the growth in urine. At pH 7.5 growth was enhanced in all three media. The addition of urea to any of the media had little effect. Three per cent sodium or potassium chloride made the urine hypertonic (specific gravity, 1.025) and suppressed bacterial growth. Sodium was more toxic in the pyelonephritis-urine, but ionic differences were otherwise inapparent. Neither glucose nor lactose in a concentration of 0.1% increased growth significantly. Albumin improved growth in salt solution, and 10% serum in Hank's solution supported 80% of maximal growth. In contrast serum did not supplement urine as a growth medium. It can be assumed

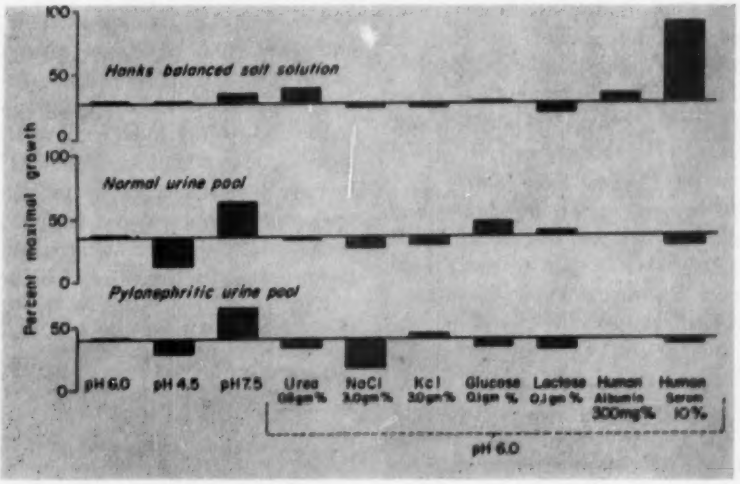

Fig. 3.—Influence of composition of urine on the growth of Escherichia coli.

TABLE 4.—*Rate of Bacterial Growth in Various Media*

Treatment of Medium	Maximal Growth After 3 Hr. Incubation, %					
	Hank's Salt Solution		Normal Urine		Pyelonephritis Urine	
	E. Coli	Enterococcus	E. Coli	Enterococcus	E. Coli	Enterococcus
pH 6.0	0	0	9	6	12	12
pH 7.5	1	0	14	10	25	22
pH 4.5	2	0	3	2	4	2
pH 6.0 + urea 0.5 gm./100 cc.	8	0	10	8	10	12
pH 6.0 + NaCl 3.0 gm./100 cc.	6	0	7	0	4	4
pH 6.0 + KCl 3.0 gm./100 cc.	4	0	7	2	4	4
pH 6.0 + glucose 0.1 gm./100 cc.	0	0	40	46	26	34
pH 6.0 + lactose 0.1 mg./100 cc.	0	0	14	8	13	11
pH 6.0 + human albumin 0.3 gm./100 cc.	7	9	11	8	13	9
pH 6.0 + human serum 10%	9	4	13	15	17	19

that some growth factors were limiting in urine but present in balanced salt solution, or bacterial growth in urine was restricted by an inhibitory substance which was not neutralized by serum. Differences between the pool of normal urine and that from patients with infection were slight and of doubtful significance.

Greater differences of perhaps more importance were observed among the media with respect to the rate of bacterial growth which they supported. The data are given in Table 4. After three hours' incubation at 37 C the urine from patients with pyelonephritis adjusted to pH 6.0 or 7.5 supported one-third to one-half more growth than the pool of normal urine and achieved 12% to 25% of maximal growth, whereas only 6% to 9% occurred in normal urine. There was no growth in the salt solution. The addition of glucose to urine greatly accelerated bacterial growth, especially in normal urine, whereas lactose produced no change. Human albumin was without effect, but the addition of serum supported a definite increase in the rate of bacterial growth in urine during the first three hours.

Thus urine was an incomplete medium for bacterial growth but one in which the lag phase was brief. Growth was more rapid in urine from patients with urinary infections than in urine from well persons and was further accelerated by slight alkalinity, glucose, or serum. Growth in the urine was suppressed by acidity and hypertonic saline.

Functional changes other than the composition of the urine which have a relationship to the pathogenesis of renal infection are the hemodynamics and urine flow. Hyperemia, ischemia, and congestion appear to increase the proneness to infection.[12,46,47] The rate of urine flow and the role of the vesicoureteral reflux have recently been reviewed.[5]

Specific Host Susceptibility to Renal Infection

Knowledge of specific host defenses in the pathogenesis of renal infection is meager. Some of the possible mechanisms are listed in Table 5. Potent nonspecific antibacterial substances have been demonstrated in the urine and the secretions of the prostate gland.[48] When proteinuria is induced many of the plasma proteins appear in the urine. These include most of the components of the complement system, specific isohemagglutinins, and perhaps other antibodies and phagocyte-promoting proteins.[49]

There is no evidence for specific hypersensitivity of the kidney or damage from specific antigen-antibody reactions or autoimmune phenomena in the pathogenesis of pyelonephritis. However, both dermal hypersensitivity and circulating antibody for the invading bacteria can often be demon-

TABLE 5.—*Host Susceptibility to Urinary Infection*

I.	Nonspecific
	Urinary bacterial inhibitors
	Plasma proteins
	General debility
II.	Immunologic
	Bacterial hypersensitivity
	Antigen—antibody reactions
	Autoimmunity

strated, and they might play an undetermined role.[50,51] In sensitized animals bacterial endotoxins produce severe renal lesions.[52]

Summary

Pyelonephritis is best considered a generic term for a group of diseases with variable clinical manifestations, distinct epidemiologies, and a different pathogenesis and course. Bacterial infection with one or more of many species of micro-organisms is the common feature and the principal cause of the interstitial inflammatory reaction that characterizes pyelonephritis. Among the categories selected for this discussion perhaps least is known about the importance of specific bacterial strains and the mechanisms involved in any specific immunity of the host. A considerable number of genetic, anatomical, and functional factors that encourage renal infection have been identified. Original observations upon the role of intermittent catheterizations suggest that it can be done with a low risk of infection. Laboratory data presented support the hypothesis that the composition of the urine can make a person more vulnerable to infection by encouraging a faster rate of bacterial growth.

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Sulfamethoxypyridazine in Urinary Tract Infections

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Recently a new sulfonamide compound, sulfamethoxypyridazine, has been introduced into clinical usage which differs in several respects from currently available preparations of this group of drugs.[1] The new agent is promptly absorbed after oral administration, and the free form of the drug is very slowly excreted in the urine. This results in long-sustained high plasma concentrations of free drug with doses much lower than those required to attain similar concentrations with several other sulfonamide agents.

An important area of usage of sulfonamides is in the treatment of urinary tract infections. When they are employed for this purpose, some observers have stressed the value of high urinary concentrations of biologically active material, and this is a prominent characteristic of several sulfonamide derivatives currently available. With sulfamethoxypyridazine, however, urinary concentrations of free drug are low, often not exceeding the plasma concentration. to establish its clinical effectiveness, partic- Thus, while there are apparent advantages in using an agent which permits smaller and less frequent doses, it is of first importance ularly in view of the possible disadvantages of low concentrations of active drug in the urine.

Accordingly, a study was made of the effect of sulfamethoxypyridazine in urinary infection. Included in the investigation were observations on the distribution and excretion of the drug after oral administration, in vitro antimicrobial activity, and results of treatment of patients with urinary tract infection.

Materials and Methods

Clinical Material and Experimental Subjects. Experimental subjects were adult patients with a variety of medical and surgical diseases but without known primary renal disease. Clinical material will be described under "results."

Laboratory Procedures.—Bacteriology: Urine specimens in males were usually collected without catheterization after cleaning the glans penis with soap and water and benzalkonium chloride 1:1000. Specimens from females were obtained by catheterization. Urine specimens were cultured and the sediment was examined microscopically without delay. In addition to conventional bacteriological identification procedures colony counts were made of most specimens. Susceptibility to antibiotics was tested by the paper-disk method, with use of commercially prepared disks.* Susceptibility to sulfonamides was determined by incorporating weighed amounts of the pure drug into an agar medium † designed to prevent interference by sulfonamide inhibitors, to which had been added 5% human blood. Inocula consisted of 1:100 dilutions of overnight broth cultures applied with capillary tubes. Tests of sulfonamide activity were read after overnight incubation at 37 C, and the endpoint selected was complete, or nearly complete, inhibition of growth.

Sulfonamide Assays: Plasma and urine concentrations of the three sulfonamides ‡ studied

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* Difco, Detroit.

† Mueller-Hinton medium, Difco, Detroit.

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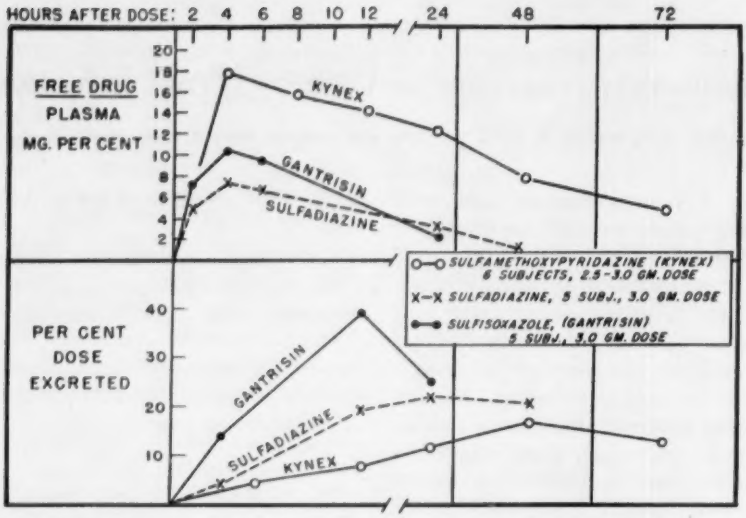
HOURS AFTER DOSE: 2 4 6 8 10 12 24 48 72
FREE DRUG PLASMA MG. PER CENT
KYNEX
GANTRISIN
SULFADIAZINE
SULFAMETHOXYPYRIDAZINE (KYNEX) 6 SUBJECTS, 2.5-3.0 GM. DOSE
X—X SULFADIAZINE, 5 SUBJ., 3.0 GM. DOSE
SULFISOXAZOLE, (GANTRISIN) 5 SUBJ., 3.0 GM. DOSE
PER CENT DOSE EXCRETED
GANTRISIN
SULFADIAZINE
KYNEX

Fig. 1.—Comparative studies of absorption and excretion of three sulfonamide drugs reveal highest plasma concentrations after sulfamethoxypyridazine. Excretion in urine is most rapid with sulfisoxazole.

were determined by the Bratton-Marshall reaction[3] with use of appropriate standards.

Results

Comparison of Plasma and Urine Concentrations of Sulfamethoxypyridazine with Other Sulfonamide Compounds.—Assays of plasma and urine following administration of single oral doses of the three sulfonamides to groups of five subjects (Fig. 1, Tables 1 and 2) reveal that sulfamethoxypyridazine yields plasma concentrations almost double those of sulfisoxazole or sulfadiazine after similar doses. While the two latter drugs were largely cleared from the plasma after 24 hours, there remained almost 8.0 mg. per 100 ml. of free sulfamethoxypyridazine after 48 hours.

TABLE 1.—*Plasma Concentrations After Single Oral Doses of Sulfamethoxypyridazine, Sulfisoxazole, and Sulfadiazine* *

Hr. After Dose	Plasma Concentration (Free), Mg./100 Ml.		
	Sulfamethoxypyridazine	Sulfisoxazole	Sulfadiazine
2 Range		3.8–15.8	2.6–7.4
Mean		7.3	4.6
4 Range	14.8–19.6	8.2–14.4	4.3–8.8
Mean	17.8	10.5	7.2
6 Range		5.8–12.8	3.9–8.0
Mean		9.6	6.4
8 Range	14.0–17.0		
Mean	15.8		
12 Range	13.4–15.4		
Mean	14.3		
24 Range	10.8–13.6	0.9–3.8	2.2–4.3
Mean	12.3	2.2	3.1
48 Range	6.0–9.3		0.8–2.4
Mean	7.9		1.4
72 Range	3.4–5.3		
Mean	4.6		
96 Range	2.4–3.4		
Mean	3.05		

* Dose: 3 gm. per subject, except 2.5 gm. to three receiving sulfamethoxypyridazine; Five subjects each drug; 0-hour specimen negative all subjects.

The accumulation in the urine of these agents reciprocated to a degree their plasma concentrations, so that an average of 77% of the sulfisoxazole dose was recovered in the first 24 hours and 45% of sulfadiazine, while only 23% of the sulfamethoxypyridazine appeared in this period. The highest group average concentration (Table 2) of free sulfisoxazole obtained during the first 24 hours was 157 mg. per 100 ml., 45.2 mg. per 100 ml. of sulfadiazine, and only 22.4 mg. per 100 ml. of sulfamethoxypyridazine.

In Vitro Antimicrobial Activity of Sulfamethoxypyridazine, Sulfisoxazole, and Sulfadiazine.—Preliminary experiments indicated that both blood and the special medium were required to disclose the highest degrees of sulfonamide activity, and in Figure 2

TABLE 2.—*Urine Excretion of Sulfamethoxypyridazine, Sulfisoxazole, and Sulfadiazine After a Single Oral Dose*

	Sulfamethoxypyridazine				Sulfisoxazole				Sulfadiazine			
Hr. After Dose	Subject	Urine Vol., Ml.	"Free" and Total, Mg./100 Cc.	Dose Recovered, Mean %	Subject	Urine Vol., Ml.	"Free" and Total, Mg./100 Cc.	Dose Recovered, Mean %	Subject	Urine Vol., Ml.	"Free" and Total, Mg./100 Cc.	Dose Recovered, Mean %
0–6 or 0–4	1*	410	7.5		6	225	448		11	540	16.0	
	2*	1,100	9.2		7	930	26		12	435	45.0	
	3*	1,340	11.8		8	690	31		13	600	5.0	
	4	320	23.0		9	400	73		14	850	16.0	
	5	1,460	8.0	3.6	10	90	316	13.6	15	320	17.5	3.7
4–12					6	1,970	84		11	915	80.0	
					7	950	100		12	1,035	87.0	
					8	1,620	56		13	890	36.0	
					9	700	204		14	1,860	30.5	
					10	170	540	39.0	15	630	66.0	19.6
6–12	1	450	30.5									
	2	500	24.0									
	3	550	44.0									
	4	1,750	24.0									
	5	2,300	8.5	8.1								
12–24	1	410	52.0		6	990	32		11	990	66.0	
	2	500	37.0		7	1,150	102		12	1,635	72.0	
	3	400	85.0		8	1,910	43		13	705	50.0	
	4	1,600	32.5		9	400	144		14	1,440	48.5	
	5	2,400	12.5	11.5	10	515	162	24.7	15	840	52.0	22.1
24–48	1	2,100	15.0						11	2,015	13.0	
	2	2,400	22.5						12	2,465	38.5	
	3	2,100	19.8						13	830	83.0	
	4	3,900	16.4						14	2,450	29.0	
	5	4,800	9.9	17.6					15	1,100	42.0	20.5
48–72	1	1,950	13.0									
	2	2,800	16.4									
	3	2,150	9.9									
	4	3,750	9.5									
	5	2,750	17.0	12.9								
72–96	1	No specimen										
	2	1,350	16.4									
	3	1,550	13.0									
	4	3,100	9.9									
	5	2,550	6.5	8.1								

* 2.5 gm. dose; others, 3.0 gm. dose.

and Table 3 are shown the results of a comparison of the activity of the three agents in this medium against 98 bacterial strains of several species. The inhibitory activity displayed by the three sulfonamides shows close correspondence in the proportion of strains which are inhibited at various drug concentrations by the three agents. It may also be seen that a somewhat larger number of strains was resistant to sulfadiazine among the higher drug concentrations. This is considered to be indicative of the relative insolubility of sulfadiazine in these ranges.

In Table 4 is shown a comparison of the in vitro activity of the three sulfonamide drugs against 104 strains of six bacterial species. Once again it is evident that these three sulfonamides possess very similar degrees of activity against these organisms.

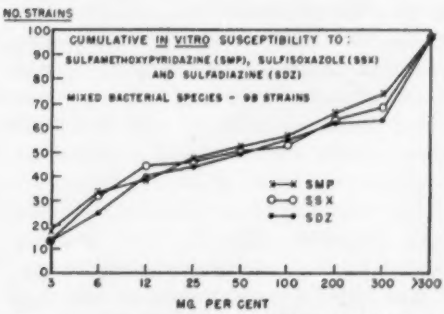

Fig. 2.—The number of strains inhibited at various drug concentrations did not vary widely among sulfamethoxypyridazine, sulfisoxazole, and sulfadiazine.

TABLE 3.—*Cumulative Inhibition of Ninety-Eight Bacterial Strains of Several Species by Sulfamethoxypyridazine, Sulfisoxazole, and Sulfadiazine*

Inhibitory Conc., Mg./100 Cc.	No. Strains		
	Sulfamethoxypyridazine	Sulfisoxazole	Sulfadiazine
3	18	13	13
6	33	32	25
12	39	44	40
25	47	46	44
50	52	50	49
100	56	53	55
200	65	66	62
300	74	68	63
>300	98	98	98

TABLE 4.—*In Vitro Susceptibility to Sulfamethoxypyridazine, Sulfisoxazole, and Sulfadiazine of 104 Strains of Six Bacterial Species*

Species (No. Strains)	Drug Tested *	Inhibitory Concentration, Mg./100 Ml. 12 and Under	25–50	100–200	300 and Over
Staphylococcus aureus (24)	SMP	54 †	29	17	0
	SSX	67	17	17	0
	SDZ	54	17	17	13
B. proteus (21)	SMP	62	5	5	29
	SSX	62	5	13	19
	SDZ	66	0	13	19
E. coli (17)	SMP	48	6	12	36
	SSX	54	0	0	46
	SDZ	42	6	0	54
A. aerogenes (23)	SMP	26	13	22	40
	SSX	31	9	22	40
	SDZ	31	9	9	49
Paracolon bacillus (12)	SMP	33	8	0	58
	SSX	33	8	8	50
	SDZ	33	0	17	50
P. aeruginosa (7)	SMP	14	0	14	70
	SSX	14	0	28	56
	SDZ	14	28	14	42

* SMP indicates sulfamethoxypyridazine; SSX, sulfisoxazole; SDZ, sulfadiazine.
† Per cent of strains inhibited.

In Figure 3 is shown a graph of the effect of sulfamethoxypyridazine against the organisms described in Table 4. They are arranged by species in descending order of susceptibility to the drug. It may be seen that the staphylococci, the only Gram-positive cocci represented, were the most highly susceptible, followed rather surprisingly by strains of Bacillus proteus. Escherichia coli was next, and these organisms were only slightly more resistant than the B. proteus. Aerobacter aerogenes strains were highly resistant, as were a small group of paracolon bacilli and Pseudomonas. A number of enterococci were examined in this study (not shown) and were generally not inhibited by the three sulfonamide drugs. These organisms grew slowly, however, and accurate estimate of drug effect was difficult. It should be emphasized that the inhibitory concentrations described in Table 4 were based on endpoints of virtual absence of growth after overnight incubation and that significant inhibition of growth was usually detectable in twofold to fourfold lower drug concentrations. This was a particularly prominent observation among resistant strains of Proteus in that they lost their spreading tendency at concentrations severalfold lower than the inhibitory concentration.

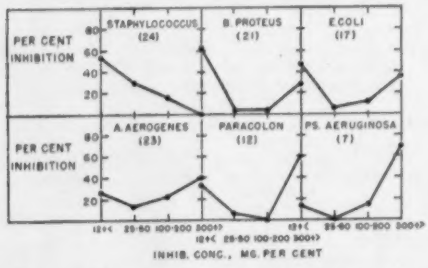

Fig. 3.—Susceptibility of 6 bacterial species to sulfamethoxypyridazine. Sulfamethoxypyridazine was most active against staphylococci, B. proteus, and E. coli and was less active against strains of A. aerogenes, paracolon bacillus, and P. aeruginosa.

Effect of Sulfamethoxypyridazine in Urinary Tract Infection.—Twenty-five patients with chronic urinary tract infection from a variety of causes were treated. Sixteen were studied as outpatients; the remainder were hospitalized. All patients exhibited heavy bacteriuria and various degrees of pyuria at the start of treatment. Symptoms of dysuria, frequency, back pain, etc. were often present but were not usually severe in these chronically ill patients. Three patients had infections associated with indwelling catheters; six had severe chronic paralytic poliomyelitis with urinary infection; five had infections following prostatic operations; four had pyelonephritis; five had chronic cystitis and urethritis, and two had carcinoma of the bladder. All of the patients had received treatment previously with antibiotics and other agents, and it was not anticipated that complete eradication of infection would follow therapy with sulfamethoxypyridazine. Although most patients exhibited symptomatology of infection which would provide a basis for measuring drug effect, greater reliance was placed on quantitative cultures of urine and careful examination of the urinary sediment before and during treatment. Experience in this laboratory has shown that the first specimens passed in the morning are likely to have higher bacterial counts than those taken later in the day. Moreover, increased fluid intake will lead to diuresis and a temporary reduction in bacteriuria. Nevertheless, serial

TABLE 5.—*Results of Treatment of Twenty-Five Patients with Urinary Infection with Sulfamethoxypyridazine*

Daily Dose, Gm.	Duration of Treatment in Wk., Range/Mean	No. Cases	Clinical			Laboratory			
			Significant Improvement	Slight Improvement	No Change	Urine Converted to Sterility	Bacteruria Significantly Reduced	Bacteruria Unchanged	Pyuria Improved
0.5	1–16/4.5	20	4*	4	12	1	1	18	4
1.0	1–5/4.5	5	3†	1	1	3	--	2	4

* First cultures: A. aerogenes, —3; P. aeruginosa, —1.
† First culture: A. aerogenes, —2; E. coli, —1.

quantitative cultures of the urine taken at approximately the same time each day after discarding overweight specimens offer a rough guide to the effect of therapeutic agents.

Perhaps as a consequence of repeated courses of treatment, strains of E. coli were infrequently isolated from the urine of these patients. Instead, 18 of the 25 patients had infection associated with A. aerogenes, either alone (7 cases) or with other bacterial species (11 cases), most often consisting of B. proteus. E. coli was present in the pretreatment culture of only three patients. P. aeruginosa or paracolon bacilli were isolated from the initial cultures of the remaining four patients.

The results of treatment of these patients are summarized in Table 5. Twenty patients received daily doses of 0.5 gm., while five patients received 1.0 gm. daily. Treatment was continued for several weeks in most cases.

Among 20 patients receiving 0.5 gm. per day of sulfamethoxypyridazine only four exhibited significant clinical improvement, and in only one did bacterial cultures become negative during treatment. It was observed among these patients that enterococci were rarely present in cultures at the start of treatment but were frequently isolated during or after treatment. These organisms were usually accompanied by Gram-negative bacilli, and in no case did they appear to be the cause of important symptomatology.

In contrast to the poor results of treatment with 0.5 gm. daily, doses of 1.0 gm. daily were associated with prompt improvement and complete clearing of urine in three of five cases, and in a fourth case pyuria diminished. Plasma determinations of free sulfamethoxypyridazine were made regularly during treatment of these patients, and a comparison of values obtained in the two dosage groups is described in Table 6 and

TABLE 6.—*Plasma Concentration of "Free" Sulfamethoxypyridazine During Consecutive Weeks of Treatment* *

Treatment Wk.	Gm./Day	No. Determinations	Mg./100 Ml.	
			Range	Mean
First	0.5	14	2.2–14.5	7.5
	1.0	4	13.2–16.2	15.2
Second	0.5	6	4.8–13.7	8.2
	1.0	3	13.0–16.4	14.6
Third	0.5	9	4.4–21.7†	10.3
	1.0	3	10.5–16.0	13.9
Fourth	0.5	10	6.0–11.1	8.7
	1.0	3	13.4–16.4	14.7
Fifth	0.5	6	3.4–11.9	7.2
	1.0	--	------	----
Total	0.5	45	2.2–21.7	8.3
	1.0	13	10.5–17.0	14.6

* Daily dose: 0.5 gm., once or twice daily. Blood samples drawn approximately 4 hr. after morning dose.
† Preexisting renal insufficiency.

Figure 4. It may be seen that among patients receiving 1 gm. daily plasma values were always within the usually described effective range for sulfonamides (10 to 17 mg. per 100 ml.), while those with the

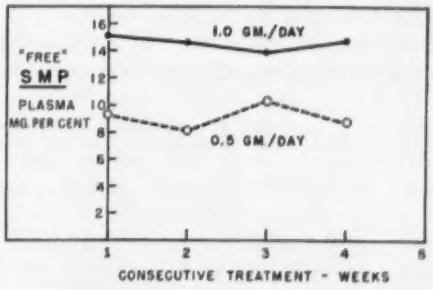

Fig. 4.—Sulfamethoxypyridazine in 1 gm. daily dose gave average plasma concentrations of 15 mg. per milliliter. Doses of 0.5 gm. resulted in plasma values of about 10 mg. per 100 ml.

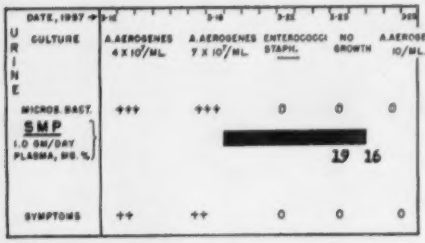

Fig. 5.—Beneficial effect of sulfamethoxypyridazine in a 23-year-old man with paralytic poliomyelitis and urinary tract infection.

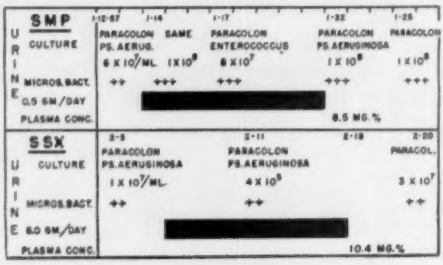

Fig. 6.—This 32-year-old man with paralytic poliomyelitis and urinary tract infection was not improved with treatment with sulfamethoxypyridazine and sulfisoxazole.

smaller dose were generally considerably lower and less consistent.

An example of a favorable therapeutic result is shown in Figure 5. The patient, a 23-year-old man with paralytic poliomyelitis and chronic urinary tract infection, was given 1 gm. daily of sulfamethoxypyridazine. During this treatment a strong positive culture of A. aerogenes became negative, pyuria cleared, and symptoms disappeared, although a later culture yielded 10 colonies of A. aerogenes per milliliter.

In an effort to evaluate further the effect of sulfamethoxypyridazine two patients who had failed to respond to this drug were further treated, one with sulfisoxazole and the other with sulfadiazine, with what were considered to be equivalent doses. The results may be seen in Figures 6 and 7, where it may be observed that there was little evidence of response to any of the three sulfonamide compounds.

Reactions to Treatment.—There was no evidence of renal toxicity in this study, despite the administration of sulfamethoxypyridazine to one patient with preexisting renal insufficiency and severe pyelonephritis.

One patient developed a morbilliform rash thought to be due to the drug which improved promptly when treatment was stopped. No further drug was given.

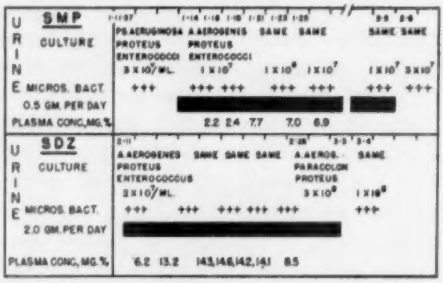

Fig. 7.—Failure to influence pyuria and bacteriuria in an 83-year-old man with cerebral thrombosis and chronic urinary tract infection (in whom an indwelling catheter was used) by treatment with sulfamethoxypyridazine and sulfadiazine.

No evidence of agranulocytosis or other hematologic toxicity was observed.

Comment

Frisk and Wassen,[3] Walker and Hamburger,[4] and Jackson and Greble[5] have reported on the use of sulfamethoxypyrid-

TABLE 7.—*Treatment of Pyelonephritis with Sulfamethoxypyridazine*

Daily Dose, Gm.	No. Cases	Result			Reference
		Good	Fair	None	
2.0	32	16*	10	6	Frisk and Wassen
1.0–2.0	10 (acute)†	10	--	--	Walker and Hamburger
1.0–2.0	6 (chronic)	4	--	2	
2.5 stat., then 0.5	28 (acute)	21	(7 unspecified)		Jackson and Greble
	28 (chronic)	8	(20 unspecified)		
Total	70 (acute)	47			
	34 (chronic)	12			

* 14 due to E. coli.
† 7 due to E. coli.

azine in urinary infections. Their results are summarized in Table 7. Seventy cases of acute and thirty-four of chronic urinary infection of various diagnostic categories were treated. The doses employed were equivalent to 1 gm. per day or greater during the first days of treatment. Two-thirds of the acute cases responded favorably, as did one-third of the chronic cases. All observers reported that infections caused by E. coli were most susceptible to treatment, while those caused by A. aerogenes generally responded poorly. It was noted that enterococci appeared in many cultures during or after treatment.

The results of therapy in the present study suggest that 0.5 gm. per day is not a satisfactory dose in chronic severe urinary tract infection. This seems understandable when it is appreciated that plasma concentrations of drug are low with this small dose, and, though not measured, it may be assumed that urine concentrations were also low. In contrast, in the present studies and in those reported by others doses of 1 gm. per day or greater were effective in the treatment of a high proportion of acute infections and to a reasonable degree in chronic infections. Moreover, in many of our own chronic cases we have had opportunity to test several antibiotics and other sulfonamides without observing any more benefit.

On the basis of all of this evidence it is our opinion that doses of sulfamethoxypyridazine which yield plasma concentrations ranging above 10 mg. per 100 ml. will prove as effective in the treatment of urinary tract infection as other sulfonamide compounds. Doses less than this, yielding correspondingly lower plasma concentrations, appear to be less effective.

The similarity of the in vivo spectrum of antimicrobial activity of the three sulfonamide drugs is in agreement with the opinion of similar degrees of clinical effectiveness of these agents. An important fact recalled by the present study is the relatively high susceptibility of B. proteus to sulfonamides. Since this is one of the few agents significantly active against this bacterial species, it is well to have this information at hand. A recent example of the beneficial clinical effect of sulfonamides against B. proteus is the report by Walker and Hamburger [4] of a patient with lung abscess due to Proteus mirabilis who responded promptly to treatment with sulfamethoxypyridazine.

It is probable that the favorable results of treatment of urinary infections with sulfamethoxypyridazine are largely due to high tissue concentrations which are derived from the plasma rather than to the relatively small concentrations of active drug present in the urine. Furthermore, it is logical to suppose that high tissue concentrations are of primary importance in treatment of urinary infections, especially in such diseases as pyelonephritis, where the lesions may be located in tissue not in contact with urine. At the same time it is recognized that more superficial infections of the urinary tract may often be controlled by urinary antiseptics which are primarily active in the urine.

Summary

Sulfamethoxypyridazine, a new sulfonamide compound, is characterized by rapid absorption after oral administration and slow excretion of the free drug from the plasma. This results in well-maintained plasma concentrations with daily doses as low as 1.0 gm., while urine concentrations of the active agent are consistently low.

The in vitro spectrum of antimicrobial activity of sulfamethoxypyridazine closely resembles that of sulfisoxazole and sulfadiazine. The three drugs were found to be most active in vitro against strains of staphylococci, Escherichia coli, and Bacillus proteus and least active against strains of Aerobacter aerogenes, paracolon bacillus, and Pseudomonas aeruginosa.

Sulfamethoxypyridazine was effective in the treatment of four of five patients with severe chronic urinary tract infection in daily doses of 1.0 gm. It was only slightly effective in the treatment of a larger series

of patients when daily doses of 0.5 gm. were used.

Miss Dorothy Moore, Mrs. Rachel Younger, and Mr. William E. Daniels provided technical assistance.

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Bacteriuria and the Diagnosis of Infections of the Urinary Tract

With Observations on the Use of Methionine as a Urinary Antiseptic

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Pyelonephritis and related infections of the urinary tract are among the most frequently encountered, most frequently undiagnosed, and most difficult to manage of all infections. The lack of clear views of the pathogenesis, diagnosis, and treatment of infections of the urinary tract is well recognized.[1-3]

A few selected data indicate the magnitude of the problem.

1. Pyelonephritis is the commonest disease of the kidneys at autopsy. Active pyelonephritis has been found in 10% to 20% of autopsies in several general hospitals,[4-6] and healed pyelonephritis occurs about as frequently as does active pyelonephritis.[6]

2. Pyelonephritis has been implicated, with varying degrees of evidence, in such disorders as hypertension, chronic renal insufficiency, toxemias of pregnancy, various disturbances in electrolyte metabolism, diabetes mellitus, pregnancy, and stone formation.

3. Despite the importance of this group of diseases the diagnosis of infection of the urinary tract is made in only about 20% to 30% of those who are found to have active pyelonephritis at autopsy, and the diagnosis is missed about as often in those with massive pyelonephritis as in those with minor and incidental lesions.[6]

That the classic syndrome of fever, flank pain, dysuria, and pyuria may be absent in pyelonephritis is well known, and equally well recognized is the fact that pyelonephritis frequently occurs as a smoldering chronic infection in which the diagnosis is often overlooked until too late.[7-9]

It is apparent that there is a large reservoir of unrecognized infections of the urinary tract and that if the serious consequences of pyelonephritis are to be averted, early and more precise recognition of the presence of such infections is necessary. The absence of defined clinical symptomatology and the inconstancy of pyuria in chronic active pyelonephritis led to detailed studies of the bacteriologic flora of the urine in relation to the diagnosis of urinary tract infections.[10] Many attempts have been made in the past to distinguish between true bacteriuria, defined as actual residence of bacteria within the urine of the urinary tract, and contamination, defined as the adventitious entry of bacteria into the urine during the collection of the specimen.

Most of these attempts have not received widespread acceptance because the criteria for distinguishing between contamination and bacteriuria were usually arbitrary.

We have studied the problem in about 2000 persons and advance the following generalizations.

(*a*) Urine is usually an excellent culture medium for the common pathogens of the

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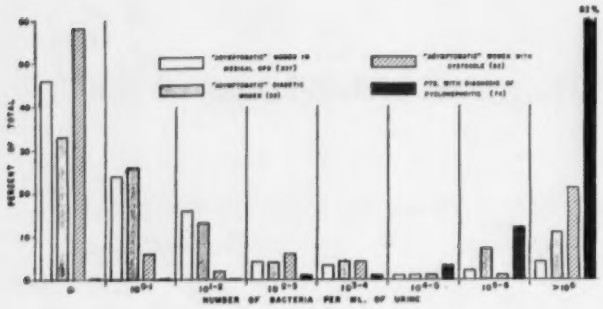

Bacterial counts in urines of various population groups.

urinary tract. If small numbers of these bacteria were to be discharged into the urine from a renal lesion they would rapidly multiply to reach concentrations of many millions of bacteria per milliliter of urine.

(*b*) If the numbers of bacteria are counted in the urines of patients in whom the house staff has diagnosed pyelonephritis (Figure), bacterial counts greater than 100,000 bacteria per milliliter are found in 95% of specimens[10]; pyuria, in about half of these. It has been known for many years that bacteria can usually be found in stained specimens of urine if infection is present. About 100,000 bacteria per milliliter must be present in urine for the stained specimens to be consistently read as positive.[10,11] If the patients have fever, flank pain, dysuria, and pyuria, more than 100,000 bacteria per milliliter of urine are almost always found. In fact, the failure to find large numbers of bacteria in the presence of the classic syndrome of pyelonephritis should raise the question of ureteral obstruction.

(*c*) The urines of 335 female patients in the outpatient department were studied (Figure), excluding those patients with symptomatic infections of the urinary tract. The urines were obtained by catheterization and cultured promptly thereafter. The patients could be divided into two groups. In one group were those with bacterial counts between 0 and 100,000 per milliliter of urine. Only about 15% of these patients had a past history of urinary tract infections, instrumentation, or inlying catheterization of the urinary tract. The bacteria that were found in the specimens obtained by catheterization of these patients usually were the common saprophytes of the urinary tract, and coliform organisms were found only occasionally. That the bacteria that were found were indeed contaminants was further indicated by the observations that when urine specimens were obtained a second time from patients with less than 100,000 bacteria per milliliter, the second counts were rarely alike.[10]

In the second group were patients with more than 100,000 bacteria per milliliter of urine; 55% of these had a history of past urinary tract infections, instrumentation, or inlying catheterization. These patients were repeatedly found to have bacterial counts greater than 100,000 per milliliter of urine, and the organisms found were almost always the common pathogens of the urinary tract. These patients were therefore considered to have true bacteriuria.

About 1% of patients had bacterial counts between 10,000 and 100,000 per milliliter of urine.[10] When the counts were repeated with use of a first morning specimen of urine the distinction between contamination and bacteriuria was readily made.

In general, then, patients with more than 100,000 bacteria per milliliter of urine may be regarded as having true bacteriuria. With excessive hydration, antibacterial therapy, and similar special circumstances the quantitative approach becomes less valid.[2] In most instances, however, the presence of 100,000 or more bacteria per milliliter of urine can be regarded as an index of bacteriuria, and surveys of the incidence of

TABLE 1.—*Occurrence of Bacteriuria in Various Population Groups at the Boston City Hospital* *

1. 6% of 337 females in medical outpatient department
2. 4% of 102 males in medical outpatient department
3. 18% of 54 diabetic females in outpatient department
4. 5% of 37 diabetic males in outpatient department
5. 11% of 152 pregnant females at term
6. 23% of 52 females with cystocele
7. 98% of 100 patients with inlying catheters for 96 hr.
8. 2% of 350 patients, previously without bacteriuria, who underwent single catheterization

* Data modified from Kass[10].

bacteriuria in various population groups may be undertaken (Table 1).

We have found, for example, that 6% of women in the medical outpatient clinic of the Boston City Hospital and 5% of men in this clinic have true bacteriuria.[10] In addition, bacteriuria is found in 18% of diabetic outpatient females, 5% of diabetic outpatient males, 11% of pregnant women coming to term, 23% of women admitted to the gynecologic service for repair of cystoceles, 30% of women and 12% of men on the medical wards, 70% of men on the genitourinary wards, and last, but not least, 98% of patients harboring inlying catheters for more than 96 hours. The latter is true despite the fact that most of these patients were receiving prophylactic antibacterial therapy and many were receiving one or another type of intermittent lavage of the catheter and bladder.

In the course of these studies it has also been found that the likelihood of inducing bacteriuria after single catheterization in women is 2% to 4%.

The data thus far presented involved obtaining urine by catheterization of females and "clean voiding" in males. In further study it was found that specimens voided into sterile containers could be obtained from females and from children and used for quantitative study. Thus, not only is catheterization, with its physical and psychologic hazards, usually avoided, but also the task of following the effect of antibacterial treatment on the urinary flora of patients with infection becomes much simplified.

Staining the urine for bacteria is about 80% reliable.[10] In voided specimens artifacts consisting of epithelial cells with adherent bacteria may appear and do not indicate true bacteriuria. The correlation between bacterial counts over 100,000 in clean voided and in catheterized specimens from the same person is over 95%. However, it is probably wise at present to insist on at least two counts of different voided specimens from the same patient, if this is possible, before the presence of bacteriuria can reliably be established using voided specimens.

The meaning of such bacteriuria is still not entirely clear. As previously noted, more than half of the patients with bacteriuria have a past history that indicates some injury to the urinary tract. Recently we have found that at autopsy bacteriuria occurs in 40% of autopsies and that there is a decided relationship between the occurrence of bacteriuria and of active pyelonephritis.[6] Thus, 14 of 40 patients with bacteriuria had active pyelonephritis (Table 2). Only 3 of 60 patients without bacteriuria had this lesion, and these 3 patients were known to have received intensive antibacterial therapy before death. There were three instances of cystitis without pyelonephritis, and all occurred in patients with bacteriuria. Bacteriuria was not a feature of healed pyelonephritis, as might be expected, and occurred much more often in patients who had undergone inlying catheterization than in those with single catheterization (Table 3).

TABLE 2.—*Pathological Lesions of the Urinary Tract in Relation to Bacterial Counts of the Urine at Autopsy*

Lesion	Bacterial Counts/Ml. Urine	
	$>10^5$ (40 patients)	$<10^4$ (60 patients)
Acute or chronic pyelonephritis	14	3
Focal or diffuse healed pyelonephritis	5 (1)*	13 (1)
Acute pyelitis	2 (2)	0
Chronic pyelitis	1	0
Acute cystitis	6 (3)	0
Chronic cystitis	1 (1)	1
Benign prostatic hypertrophy	9 (4)	17

* The figures in the parentheses indicate the number of patients in the respective group with active pyelonephritis. The data are modified from MacDonald, Levitin, Mallory, and Kass[6].

TABLE 3.—*Relationship of Catheterization During the Last Hospital Admission to Bacterial Counts in the Urine and Pyelonephritis at Autopsy*

	Total No.	Bacteria/Ml. Urine				Acute & Chronic Pyelonephritis (17 Patients)*	
		>10^5 (40 Patients)		<10^5 (60 Patients)			
		No.	%	No.	%	No.	%
Catheterizations	45	29	73	16	27	13	77
Inlying	18	16	40	2	3	8	47
Single	27	13	33	14	23	5	29

* There were three additional patients with acute cystitis alone; two of these underwent inlying catheterization and one, single catheterization. From MacDonald, Levitin, Mallory, and Kass[4].

A few additional diagnostic points may be mentioned briefly:

1. If cultures from a patient repeatedly yield Aerobacter, Proteus, Pseudomonas, or enterococci that patient will usually have undergone instrumentation or inlying catheterization of the bladder, generally in association with the "prophylactic" use of antibacterial agents.[2]

2. If a population, such as pregnant women, with a relatively high incidence of asymptomatic bacteriuria and of pyelonephritis is studied, bacteriuria is found to be present weeks or months before the development of frank symptoms.

In preliminary observations it has been found that if bacteriuria is eliminated during pregnancy by the use of a long-acting sulfonamide or by other antibacterial agents no pyelonephritis is encountered, whereas about 40% of pregnant women with bacteriuria who are given placebos develop clinical evidence of urinary tract infection before term. Almost all of these infections are due to Escherichia coli, and most of them are not difficult to control.

3. Bacterial counts of the urine have been of value in the management of chronic infection. These infections are extremely difficult to control, and bacteriologic cure probably does not exceed 10% in patients with chronic infections of the urinary tract. However, even if a cure cannot be achieved, the bacteriologic counts in the urine, which are generally about 10,000,000 or more in such patients, may be lowered to 1000 to 10,000. When dysuria is present, such lowering of the bacterial count frequently affords symptomatic relief. Whether or not the maintenance of a lower level of bacteriuria is beneficial in terms of possible renal damage is under investigation at present.

Several means exist for suppressing bacterial multiplication in the urinary tract and achieving lower bacterial counts in the urine. Sulfonamides are frequently effective. However, resistance may emerge rapidly, and there are serious questions about long-term toxicity. Nitrofurantoin has promise as a long-term suppressive agent, but we have not yet studied this drug extensively for this purpose and cannot pass adequate judgment. Methenamine mandelate is relatively nontoxic, and resistance of bacteria to this drug has not been a prominent clinical problem. However, methenamine mandelate has the serious drawback that its activity is dependent upon the urinary pH and that as the pH rises the activity of methenamine mandelate falls off sharply.[2,11] The usual methods for maintaining low urinary pH, such as the administration of ammonium chloride, are effective for only a few days because of renal adjustment to the acid load, with increased excretion of ammonia.

A more efficient means for acidifying the urine has recently been studied in our laboratory. Hunt[12] has observed that the inorganic sulfate content of urine plays a larger role in control of urinary pH than has generally been appreciated and that the feeding of methionine leads to oxidation of its sulfur to sulfate, which is then excreted in the urine, lowering the urinary pH. We have found that when methionine, in doses of 12 to 15 gm. per day, is added to the normal diet, the urine pH may be lowered to 4.5 to 5.0 and kept at this level for months in patients with adequate renal function. The bacterial

counts in the urines of patients with chronic urinary tract infections are reduced about one-thousand-fold in consequence of the administration of methionine alone, and occasionally complete eradication of the bacteria may occur. This reduction in the urine bacterial count appears to be due to the appearance in the urine of an as yet unidentified substance, probably a metabolite of methionine, that is bacteriostatic at pH 5.0.

If methenamine mandelate is given with methionine, the bacterial counts are usually lowered from about 10^8 bacteria per milliliter of urine to 10^3 to 10^4 bacteria per milliliter of urine. The combination of methionine and methenamine mandelate is generally well tolerated, although occasionally epigastric burning may occur. The lowering of bacterial counts of the urine is usually accompanied by relief of dysuria and similar symptoms if these were present.

The mechanism of action of methionine in achieving these effects is not yet clear and is under study. So active is the sulfate ion as a urinary acidifier that even alkaline urines of patients with Proteus infections can usually be made acid and the infection brought under control. Whether this type of regimen will be of value in the management of staghorn calculi and similar concretions that are peculiar to alkaline urine remains to be seen. We have not previously encountered an agent that could acidify the urine in severe Proteus infections of the urinary tract and are exploring the therapeutic possibilities in the long-term management of chronic infections of the urinary tract.

Summary

Bacterial counts of the urine permit the separation of contamination from true bacteriuria. Bacteriuria is found in many asymptomatic persons, and its incidence is increased in those population groups known to have an increased incidence of clinically detectable pyelonephritis. Pyuria is frequently absent when bacteriuria and pyelonephritis are present. Bacteriuria and pyelonephritis are related phenomena at autopsy, and preliminary evidence indicates that bacteriuria may be present for months before symptoms appear. Bacteriuria is often related to instrumentation and inlying catheterization of the urinary tract; single catheterizations are much less likely to induce infections. Voided specimens of urine are suitable for bacterial counts and yield valuable information which frequently may eliminate the need for catheterization.

A new use for the amino acid methionine is described. The feeding of 12 to 15 gm. of methionine leads to a marked decrease in the urinary pH and the appearance of an as yet unidentified bacteriostatic substance in the urine, with lowering of the urinary bacterial counts. At the low urinary pH values that are obtained the activity of methenamine mandelate is increased, and urinary bacterial counts may be lowered from initial levels of 10^8 or more bacteria per milliliter to maintenance levels of 10^3 to 10^4 bacteria per milliliter of urine.

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The Use of Androgens and Estrogens and Their Metabolic Effects

A Review of the Prolonged Use of Estrogens and Androgens in Postmenopausal and Senile Osteoporosis

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I. Introduction

Postmenopausal osteoporosis is not generally recognized as a common cause for back pain. Even when recognized it is often accepted as the normal state of the spine for the age. Finally, even when postmenopausal osteoporosis is recognized and the need for therapy appreciated, effective therapy is withheld on the bases that osteoporosis is a self-limited disease, that hormone therapy is dangerous, particularly in regard to stimulation of cancerogenesis, and that hormone therapy is too complicated for general use. It has been our experience that osteoporosis is a common disease state of postmenopausal women, that it may produce severe and disabling back pain, and that estrogen and androgen therapy is effective, safe, and simple. This paper reviews the nature of osteoporosis, summarizes the published balance studies in which estrogen and androgen therapy can be evaluated, and indicates the highlights of our own experience in the prolonged estrogen treatment of approximately 200 postmenopausal women.

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II. Description of Osteoporosis

Osteoporosis is a pathological state in which the bone mass is decreased and the bones become spontaneously painful and are readily broken. Osteoporosis seen in postmenopausal women and senile men and women is a disorder of all bones but is most manifest in the spine. It is postmenopausal and senile osteoporosis which accounts for the common finding of thoracic kyphosis in middle-aged women and the frequent occurrence of fractured wrists and hips after only moderate trauma in middle-aged women and senile persons. The characteristic radiological features of osteoporosis involving the spine are (1) collapse of vertebral bodies with anterior wedging, (2) expansion of the intervertebral discs, (3) increased contrast between the density of the end-plates and the density of the substance of the vertebral bodies, (4) decreased radiodensity of bone, and (5) increased trabecular markings. Decreased radiodensity of bone alone is not a reliable sign of osteoporosis, since the apparent bone density on a radiograph depends upon the thickness of the patient's

soft tissues, the amount of x-ray used, and the physical characteristics of film development. To date it has not been possible to devise a radiographic method of assaying bone density of the spine or other major bones. An increase in trabecular markings is sometimes noted in osteoporosis, whereas in osteomalacia and osteitis fibrosa generalisata trabecular markings are characteristically absent. It is likely that asymptomatic and then painful thinning of the vertebrae often occurs before the diagnostic radiographic signs of osteoporosis appear. Bartter [1] has recently published an excellent review of all types of generalized osteoporosis and has discussed the differential diagnosis.

Albright [2] has classified osteoporosis as the bone disease which results from too little bone matrix formation rather than from faulty calcification of bone or from excessive bone resorption. The serum calcium, phosphorus, and alkaline phosphatase are normal in postmenopausal and senile osteoporosis. Osteoporosis is a difficult condition to diagnose histologically. Whatever bone is present in the biopsy specimen is of normal structure and normally calcified (compare osteoid borders of trabeculae in osteomalacia). There is simply less bone mass and more marrow space between bone trabeculae. The individual bone trabeculae are thin; however, this feature is difficult to appreciate, since the thickness of trabeculae varies greatly from person to person, depending upon body weight and physical activity. Bone-forming osteoblasts are few in number and probably reduced, but again this is difficult to establish, since osteoblasts are normally rather sparse in adult bone. Osteoclasts are rare in osteoporosis; this finding is useful in ruling out excessive resorption as the cause for thin bones (compare osteoclasts and fibrous marrow in osteitis fibrosa generalisata).

III. Course of Osteoporosis

Since osteoporosis progresses rapidly during its early course and more slowly later, it has been suggested that osteoporosis is a "self-limited condition" for which treatment is unnecessary. This phrase usually describes a disease state which spontaneously reverts to normal. Postmenopausal osteoporosis does not spontaneously revert to normal. We have no data to demonstrate the natural course of untreated postmenopausal or senile osteoporosis over 15 to 20 years. However, there is an idiopathic form of osteoporosis for which there is no therapy

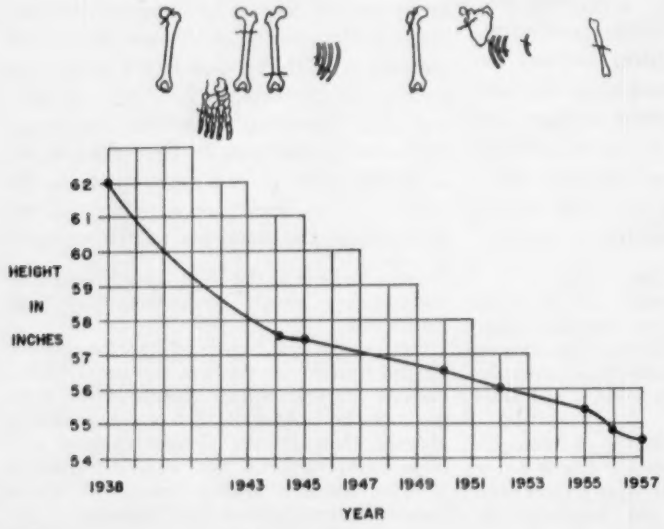

Fig. 1. — The clinical course of a patient with idiopathic osteoporosis. Above are indicated the sites of fractures at the dates indicated below. Also shown are the recorded heights of this patient over the 19 years of progressive osteoporosis. The urinary calcium excretion (not shown) was high during the early course of osteoporosis but subsequently was not dramatically increased.

and whose course illustrates the progressive nature of severe osteoporosis. Figure 1 illustrates schematically the clinical course of one such well-studied [3] patient with idiopathic osteoporosis. This woman enjoyed excellent health until age 23 (1938), when she first noted pain in both feet. Over the next 19 years she fractured most of the major bones in her body after minor trauma. Since osteoporosis most prominently involves the spine and produces collapse of the vertebral bodies, the simplest way to follow the course of osteoporosis in such a patient is to measure her height. Figure 1 illustrates the gradual loss of approximately 8 in. in height of this patient over 19 years. In Figure 2 the outline of her vertebral bodies as seen in lateral spine x-rays of 1945, 1950, and 1953 has been traced. Note the gradual increase in kyphosis and collapse of vertebrae, better appreciated as a loss of total length of the vertebral column than as a change in any individual vertebral body. This patient with idiopathic osteoporosis illustrates the point that osteoporosis does cease to progress after many years and in that sense is a self-limited disease. It progresses slowly, however, only after the bones have become painfully thinned, after disabling loss of height, and only at the cost of further easy fractures.

Fig. 2.—Superimposed tracings of the vertebral outlines as seen in radiographs of 1945, 1950, and 1953 in a patient (same as Fig. 1) with idiopathic osteoporosis. The lumbar vertebrae have been aligned. The radiographic technique and posture may not have been identical in the three radiographs. Note the increasing kyphosis and loss of height equivalent to at least two vertebral bodies, whereas the changes in individual vertebrae were relatively inapparent.

IV. Treatment of Osteoporosis

Since osteoporosis results from too little protein bone matrix formation and since all the bone present is well calcified, this condition is not favorably influenced by increased calcium intake. For similar reasons vitamin D, which increases the absorption of calcium, is without benefit in osteoporosis. The most important factor in stimulation of osteoblastic activity and maintenance of bone structure is the stress and strain of physical activity. Hence immobilization in a cast or in a back brace, while it may give temporary relief from the pain of an acute fracture, tends to diminish further the rate of bone formation and to intensify the degree of osteoporosis. Indeed, patients with postmenopausal and senile osteoporosis should be encouraged by every means possible to maintain activity to the point of discomfort. Osteoporosis is another condition in which it is now recognized that activity and exercise are beneficial rather

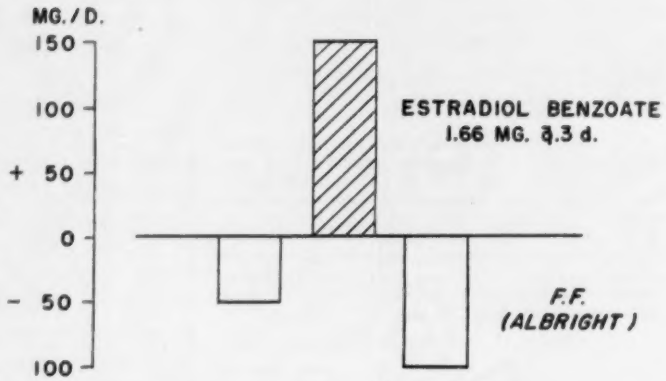

Fig. 3.—Calcium balance during estrogen therapy of postmenopausal osteoporosis. This is the only balance study[6] in which significant calcium retention has been demonstrated with estrogen therapy and in which there are suitable control periods before and after therapy. (Owing to the slow adaptation of the calcium balance in some patients the significance of any change on therapy is increased by a postcontrol in which the calcium balance returns to the level of the forecontrol.) At low levels of calcium intake the retention of 100 mg. of calcium daily is a significant finding; if this rate continued over a year's time it would account for the deposition of approximately 36 gm. of calcium, or 3% of total bone mass. Since loss of bone and new bone formation may be more marked in certain areas, such as the spine, such retention may be even more significant than these figures suggest. In this chart and those which follow the columns represent the average net balance (intake versus urinary plus fecal excretion) of the forecontrol immediately preceding therapy, of the balance during the maximum response to therapy, and of the balance at the end of the postcontrol. An effort has been made to avoid inclusion of data from periods of transition. The critical reader is referred to the original studies for further details of these studies.

than detrimental. Since bone matrix is composed of protein, just as is muscle, a normal intake of protein and maintenance of good nutrition is essential in the treatment of postmenopausal and senile osteoporosis.

V. Balance-Study Data on Treatment of Osteoporosis

In 1940 Albright[4] presented the first evidence from balance studies that estrogens and androgens improved the calcium balance

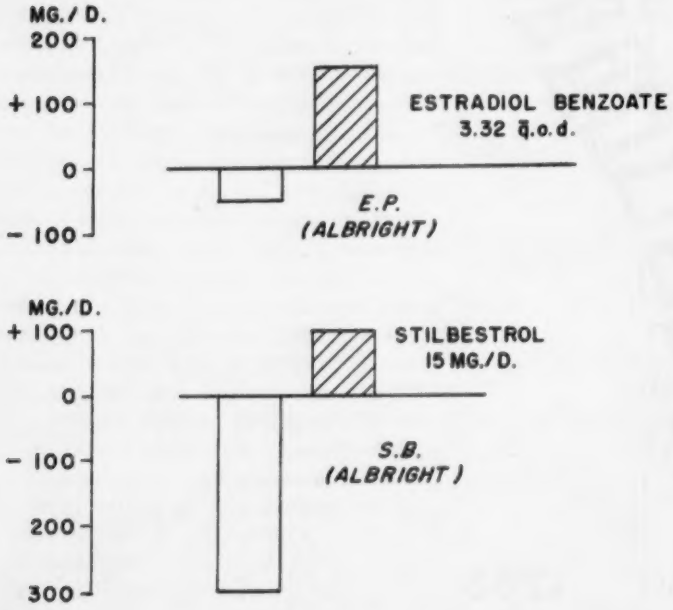

Fig. 4.—Calcium balance during estrogen therapy of postmenopausal osteoporosis. Note that calcium retention was obtained with estradiol benzoate[6] and with diethyl stilbestrol.[6] No after-control periods are available for comparison. In Patient S. B. 3 mg. stilbestrol daily produced more calcium retention than did 1 mg. daily but not more than 15 and then 30 mg. daily.

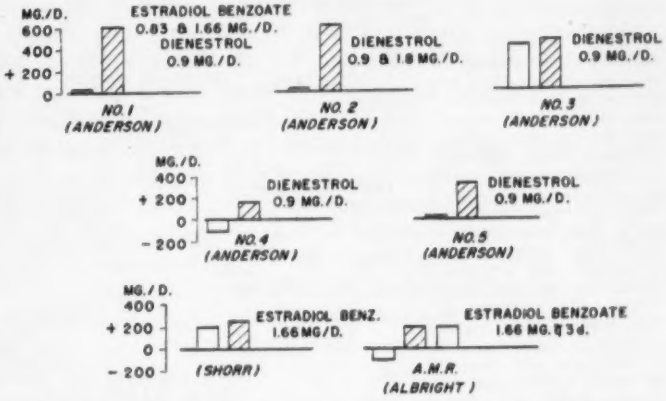

Fig. 5.—Calcium balance during estrogen therapy of postmenopausal osteoporosis. In these five balance studies of Anderson[8] both the naturally occurring estrogen estradiol and the synthetic estrogen dienestrol produced retention of 170 to 600 mg. of calcium daily in four of five patients with postmenopausal osteoporosis. No after-controls are reported to confirm the effect of therapy. The difference in calcium balance between the fore-control and treatment period in Shorr's[6] study may not be significant. (Shorr's other published balance studies on the effect of estrogen and androgen therapy of postmenopausal osteoporosis have not been included, since they are complicated by simultaneous strontium administration.) In Reifenstein and Albright's study[6] calcium retention occurred with estradiol benzoate therapy, but the significance of this change is difficult to evaluate, since the effect did not wear off during the prolonged after-control. (The duration of effect on calcium metabolism of estrogen and androgen in postmenopausal osteoporosis is not established.)

of patients with osteoporosis. Figures 3 to 8 summarize in a much simplified fashion all the balance studies reported to date concerning the effect of estrogens and androgens in postmenopausal and senile osteoporosis. In 13 of the 15 published balance studies significant calcium retention was produced by estrogen therapy in the postmenopausal woman with osteoporosis and by testosterone therapy in the senile man with osteoporosis. The evidence for calcium retention in the postmenopausal woman treated with testosterone is less convincing; no balance data are available on less than masculinizing doses of testosterone. There is little evidence of significantly greater calcium retention with combined estrogen and androgen therapy in the postmenopausal woman, although this additive effect was observed in a man with senile osteoporosis studied by Albright.

VI. Present Therapeutic Program

The above observations form the basis of our program for the treatment of postmenopausal osteoporosis which may be summarized as follows: diethylstilbestrol, 1 to 3

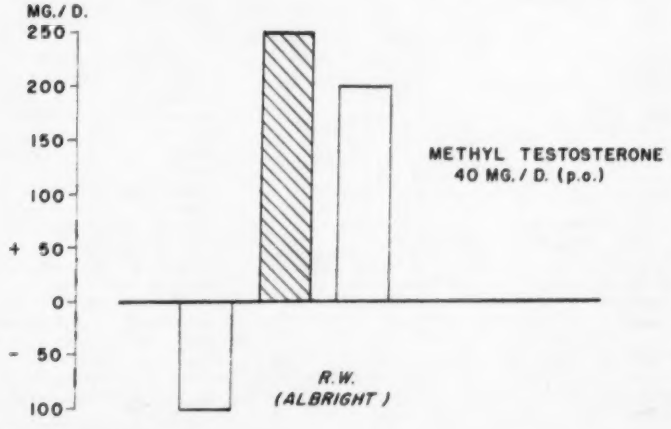

Fig. 6.—Calcium balance during androgen therapy of postmenopausal osteoporosis. This is the only published balance study[8] which illustrates that an androgen, methyltestosterone 40 mg. daily by mouth, produces calcium retention in postmenopausal osteoporosis. This dose of methyltestosterone would be virilizing in most women. The retention of 250 mg. of calcium daily is made less conclusive by the observation that the patient retained the same amount daily throughout the prolonged after-control with no medication.

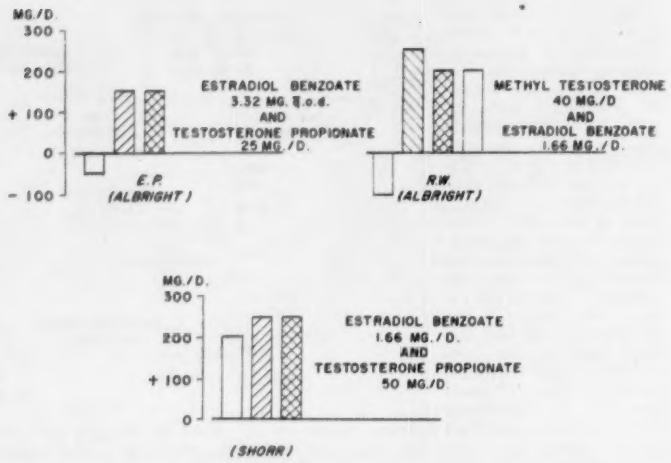

Fig. 7.—Calcium balance during estrogen-androgen therapy of postmenopausal osteoporosis. In these three balance studies estrogen and androgen were administered to women with postmenopausal osteoporosis. In each instance calcium retention occurred and ranged from 50 to 250 mg. per day. However, in the first study[8] the addition of testosterone to estrogen did not increase the rate of retention, and there is no after-control. In the second study[6] the after-control does not differ from the treatment periods with androgen and androgen plus estrogen, and in the third study[7] the already positive balance of the forecontrol is increased only slightly by androgen and then estrogen therapy in addition.

mg. daily, is given for 4 to 5 weeks and discontinued for 7 to 10 days; it is then resumed in a cyclical fashion. Such intermittent or interrupted estrogen therapy is necessary to permit desquamation of the proliferated endometrium and to prevent the development of metropathia hemorrhagica.[10] Such intermittent estrogen therapy also mimics the normal cyclical pattern of estrogen secretion and avoids the pattern of continuous estrogen secretion seen in patients with granulosa-cell tumors, with the associated high incidence of cervical and endometrial carcinoma. Since diethylstilbestrol is poorly tolerated by some postmenopausal women, we often substitute the best-tolerated estrogen, Premarin (conjugated estrogenic substances), in doses of

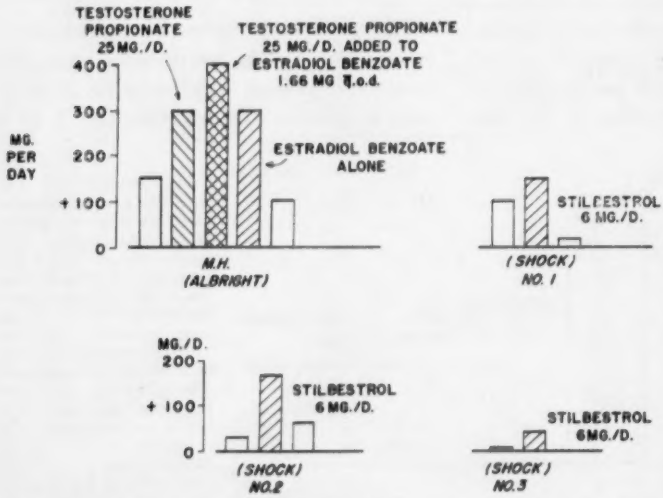

Fig. 8.—Calcium balance during therapy of senile osteoporosis in men. Balance studies in four men with senile osteoporosis are summarized. In the first of these Albright demonstrated[8] that androgen (Bartter[7] has recently published a balance study which demonstrates calcium retention with androgen administration to a male patient with eunuchoidism and osteoporosis.) produced significant calcium retention, which is increased still further with androgen plus estrogen. During the after-control the calcium balance returned to only slightly positive, an observation which validates the effectiveness of the estrogen and androgen therapy. The last three studies[9] by Shock illustrate the retention of 40 to 100 mg. calcium per day in three elderly men with osteoporosis (In this same paper diethylstilbestrol did not produce significant calcium retention in three senile men without osteoporosis.) treated with 6 mg. of diethylstilbestrol daily. In the third study by Shock the after-control was in balance.

1.25 to 5 mg. daily in a similar cyclical fashion. We do not routinely administer testosterone to postmenopausal women, since more than 5 mg. of methyltestosterone daily often produces undesirable and sometimes irreversible masculinization, with deepening of the voice, facial hirsutism, acne, and excessive stimulation of libido. We have added testosterone therapy to estrogen therapy of the postmenopausal woman only in the senile, severely debilitated, anoretic, or extremely osteoporotic person. We have treated senile men with osteoporosis with 30 mg. of methyltestosterone daily by Linguet, or buccal tablet. The development of gynecomastia and loss of libido and potentia in the man treated with significant amounts of estrogen often limits the use of estrogens in the treatment of senile osteoporosis in men. Its use has been reserved for those persons with extreme osteoporosis. Estrogens and androgens are prone to cause salt and water retention and mild to moderate edema in older patients. This can often be prevented or corrected with salt restriction and diuretics. Estrogen-withdrawal menstruation is not a problem if the likelihood and reasons for this phenomenon are explained to the patient. Careful examination is made before therapy and at regular intervals for breast, cervical, endometrial, and prostatic malignancy.

In our experience the prolonged administration of estrogens to postmenopausal women always relieves the hot flashes characteristic of the menopause and often causes a striking return to normal of emotional stability, sleep patterns, and sense of energy. These changes are impossible to quantitate but constitute such an important dividend of estrogen therapy of postmenopausal osteoporosis that we have accepted them as sufficient reason for the general use of prolonged estrogen replacement of the postmenopausal woman.

VII. Clinical Results with Prolonged Estrogen Therapy for the Menopause and Postmenopausal Osteoporosis

During the past year we have reviewed the records of approximately 200 postmenopausal women treated * by Dr. Fuller Al-

* Approximately half the patients were treated for postmenopausal osteoporosis; the remaining patients were treated for other menopausal symptoms.

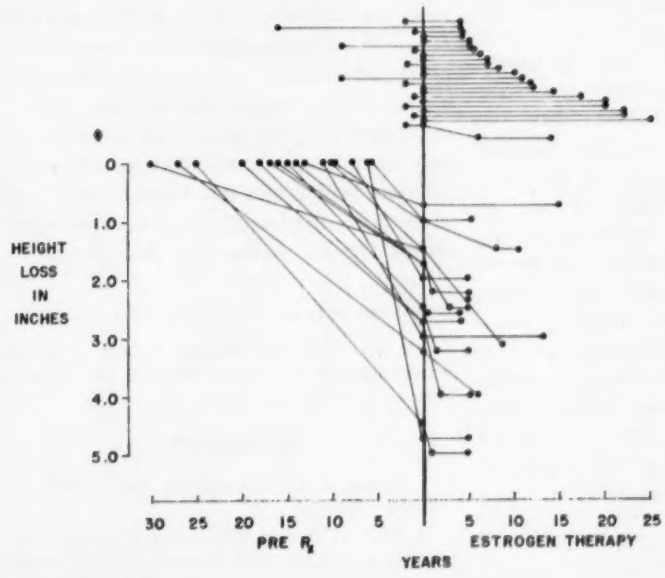

Fig. 9.—Loss of height due to osteoporosis of 40 women after the menopause before and after estrogen therapy. The heavy vertical line indicates the beginning of estrogen therapy. The collection of dots above represents women treated for the menopause without osteoporosis; the dots below connect the heights of women with postmenopausal osteoporosis.

bright and his associates for 1 to 20 years with estrogen therapy. Figure 9 illustrates the recorded heights during prolonged follow-up of 40† patients treated for 4 to 20 years with estrogens. Note that in general the longer the interval between the menopause and the onset of therapy the greater the loss in height. Note that there has been little or no further loss of height after several years of estrogen therapy. Note further that those patients treated with estrogens at the time of the menopause have failed to develop loss of height. Needless to say, some of the women in the latter group might not have developed significant loss of height due to osteoporosis even without therapy, since osteoporosis is a common but not a universal development in the postmenopausal years. Relief of back pain usually occurred after several months of estrogen therapy.

Serial radiographs of approximately 75% of the patients in this series who did not have heights recorded have shown lack of further progression of osteoporosis with prolonged estrogen therapy. Careful review of radiographs made with standard techniques after 5 to 20 years of estrogen therapy in this series has failed to demonstrate a single instance of increase in bone density. Thus estrogen therapy may stop the progression of osteoporosis but apparently cannot restore the osteoporotic bone to a completely normal radiographic status.

In the past the single greatest objection to prolonged estrogen therapy of the postmenopausal woman has been the fear of development of cancer in the breast, cervix, and endometrium stimulated over an abnormal period of time. In a series of approximately 200 female patients followed for a total of approximately 1100 patient-years of estrogen therapy only 4 instances of genital carcinoma have occurred, as follows: endometrium, 1 (discovered after 6 years of estrogen therapy); breast, 0; cervix, 0; cervix (in situ), 1 (discovered after 1 year of estrogen therapy); ovary,‡ 2 (discovered after 1 year and 5 years of estrogen therapy). Since these patients were all in the "cancer age group," this appears to be a low incidence of genital cancer and does not justify the fear that prolonged estrogen therapy may be carcinogenic.

† Height measurements were not recorded on the remaining patients of the series.

VIII. Summary

In summary, attention has again been called to the common occurrence and clinical course of osteoporosis in postmenopausal women and in senile men and women. The value of height measurements as an index of osteoporosis is illustrated. In 13 of the 15 reported complete balance studies estrogen therapy produced significant calcium retention in the postmenopausal woman and testosterone produced significant calcium retention in the senile man. The available balance studies suggest that combined estrogen and androgen therapy are more effective than either alone in the senile man, but without much additive effect in the postmenopausal woman. A practical program of estrogen therapy for the postmenopausal woman and of androgen therapy for the senile man is outlined. In a series of approximately 200 postmenopausal women treated with estrogen for 1 to 20 years the progress of osteoporosis was arrested in nearly all instances, as judged by measurements of total height and by radiographic examination of the spine. The incidence of carcinoma of the breast, cervix, and endometrium was low in this treated group and should allay the fear that prolonged estrogen therapy produces cancer of these tissues in women.

Massachusetts General Hospital (15).

‡ It is unlikely that estrogen therapy is related to development of ovarian cancer, since estrogen does not stimulate the ovary.

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Observations on the Role of Androgens and Estrogens in Body Balance

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The increased growth of the body as a whole at the time of sexual maturation early suggested a causal interrelationship of these two phenomena. This was further emphasized by the development of precocious puberty in association with gonadal tumors. In this situation a rapid increase in body weight and height, maturation of the musculature and skeleton, deepening of the voice, and growth of sexual hair may be observed together with precocious development of the genitalia.

When the gonadal steroids became available for study in man, Kenyon and his co-workers [1] demonstrated that testosterone propionate exerts anabolic effects on tissues other than those of the genital system. Thus a person eating a constant diet may gain as much as 9 kg. in body weight during testosterone administration, which is more than can be accounted for by growth of the genitals. Metabolic balance studies have shown that under the influence of androgenic steroid there is retention of nitrogen, phosphorus, potassium, and sulfur in the proportions which these elements are found in muscle and viscera, which is compatible with the concept that an increase in tissue mass occurred. Similarly, estrogenic steroids have been demonstrated to induce anabolic effects, although to a much smaller degree than androgens.

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From the Division of Clinical Investigation, Sloan-Kettering Institute and the Medical Service, Memorial and James Ewing Hospitals, Memorial Center.

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Metabolic Effects of Androgens

Testosterone propionate, in doses of 5 mg. per day intramuscularly, induces definite anabolic effects in hypogonadal males. Twenty-five milligrams of testosterone propionate daily yields nearly maximal effects on nitrogen retention. Although a greater retention of nitrogen occurs in hypogonadal patients, testosterone produces a definite anabolic response in normal men and women. Senescent men respond to androgenic steroids to about the same extent as young men. The anabolic effects of testosterone may continue for as long as 40 to 50 days, at which time the patient resumes nitrogen balance despite continuation of the hormone.

The biochemical mechanism by which androgens stimulate tissue anabolism is not known. Androgens do not appear to act indirectly through other endocrine glands, since androgens are effective in patients who have underfunction of the anterior pituitary gland, the adrenal glands, or the thyroid gland.[2]

Figure 1 illustrates the effects of dihydrotestosterone in an oophorectomized adrenalectomized woman with metastatic breast cancer. Positive nitrogen balance was sustained for more than three weeks, after which the patient returned to nitrogen balance despite the continuation of the hormone.

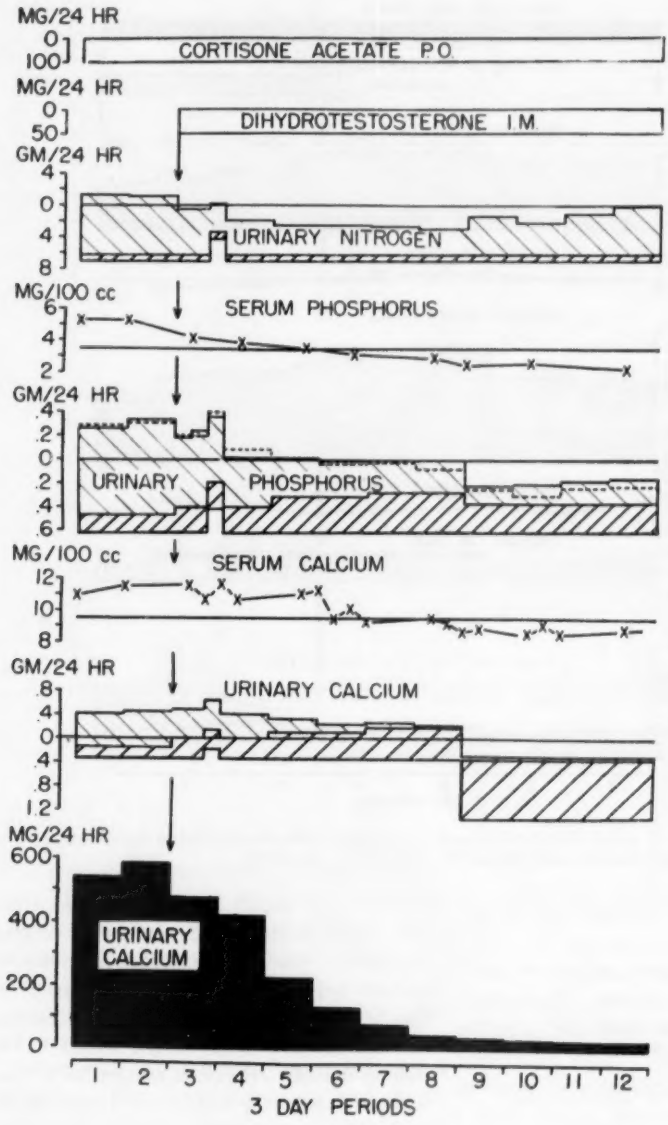

Fig. 1.—Effects of dihydrotestosterone on nitrogen, phosphorus, and calcium balances in an oophorectomized adrenalectomized woman with mammary cancer metastatic to bone. The dietary intake is plotted downward from the zero line, and the fecal and urinary output are superimposed from the intake line upward. The changes in calcium and phosphorus balances are interpreted to be due to a suppressive effect of dihydrotestosterone on the growth of the osseous tumor, resulting in decreased osteolysis.

Figure 2 presents the effects of 17-ethyl-19-nortestosterone in a woman with metastatic breast cancer who had been hypophysectomized. This patient was hypothyroid at the time of androgen administration. A positive nitrogen balance was induced and sustained during the eight days of study.

Androgen can counteract the catabolic effects of hyperthyroidism and adrenal hyperfunction. Androgens can offset the negative nitrogen balance expected from large doses of cortisone without counteracting the catabolic effects of cortisone on lymphoid tumor tissue and without opposing the antirheumatic effects of cortisone, indicating the

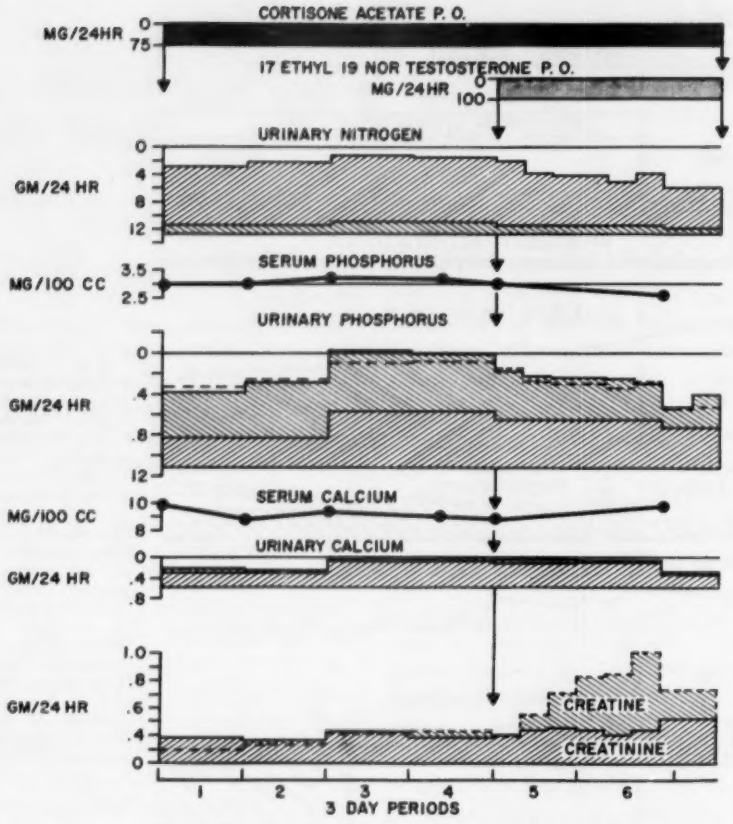

Fig. 2.—Effects of 17-ethyl-19-nortestosterone on nitrogen, phosphorus, and calcium balances in a hypophysectomized woman with metastatic mammary carcinoma.

selectivity of action of androgens on certain tissues.[3]

In selected circumstances androgenic hormones stimulate osteogenesis. Reifenstein and Albright[4] have demonstrated positive calcium and phosphorus balances in proportions consistent with deposition of bone in patients with osteoporosis.

Thus the anabolic effects of androgens involve a variety of body tissues. Animal experiments have demonstrated these anabolic effects on muscle tissue and a number of viscera.[5] In addition, androgens affect the blood-forming tissues. The anemia associated with hypogonadism is corrected by testosterone administration,[6] and polycythemia may develop in some patients.[7]

Androgens usually produce sodium, chloride, and water retention with edema formation. The degree of salt retention is variable but must be given serious consideration in patients with limited cardiac reserve.

Steroids have been sought which would induce anabolic effects on nongenital tissues without producing significant virilizing effects. Certain steroids, such as 19-nortestosterone, have been found to have relatively greater myotrophic action than androgenic effects when compared to testosterone in animal assays. As yet a complete separation of anabolic and androgenic effects has not been attained. A steroid which could induce anabolic effects without significant virilization would have obvious therapeutic advantages.

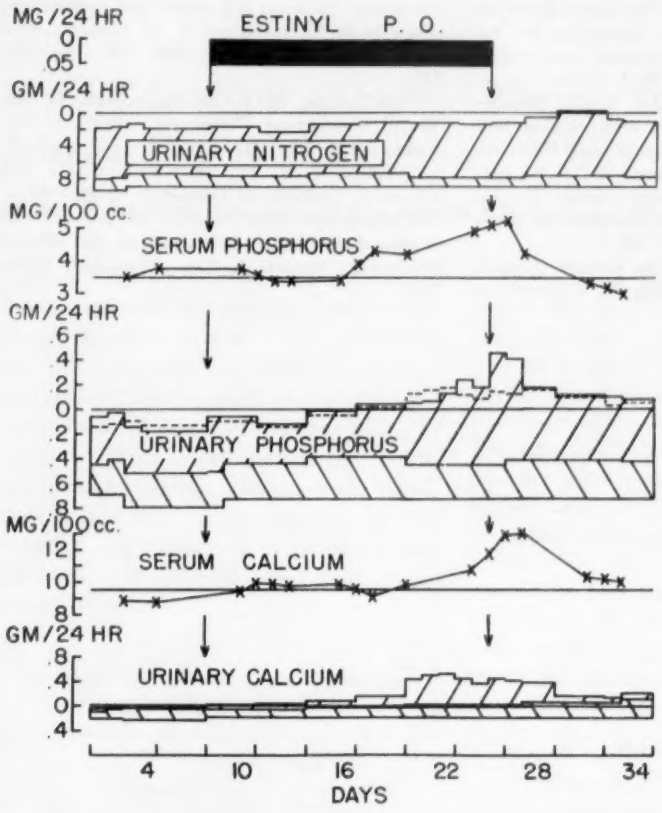

Fig. 3. — Effects of ethinyl estradiol on nitrogen, phosphorus, and calcium balances in an oophorectomized woman with mammary carcinoma metastatic to bone. The alterations in calcium and phosphorus balances are terpreted to be due to an anabolic effect of ethinyl estradiol on the osseous tumor, resulting in osteolysis.

Metabolic Effects of Estrogens

Kenyon and co-workers [1] observed positive nitrogen balances during administration of estradiol benzoate to hypogonadal males comparable to the effects obtained with small doses of testosterone. Positive nitrogen balance induced by estrogen was also observed in hypogonadal and normal women. Reifenstein and Albright [4] demonstrated a striking retention of calcium and phosphorus during estradiol benzoate administration to women with postmenopausal osteoporosis. This was interpreted as repair of defective bone matrix induced by estradiol, with consequent deposit of bone salts.

In some patients estrogen administration has failed to produce significant changes in nitrogen balance. Figure 3 presents the effects on nitrogen balance of ethinyl estradiol in an oophorectomized woman with metastatic mammary carcinoma. No significant alterations in nitrogen balance occurred.

Although estrogens have been demonstrated to induce anabolic effects in some patients, the action of estrogen on nitrogen balance appears to be less consistent than with androgen. Estrogen administration will also induce sodium, chloride, and water retention.

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Present Concepts of Steroid Therapy in Virilizing Adrenal Hyperplasia

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Since 1950, when cortisone was first used for the treatment of virilizing adrenal hyperplasia, the methods and results of therapy have been reported from time to time from this clinic [1-9] and by other workers,[10-13] and the differential diagnosis also has been discussed.[8,9] This paper summarizes briefly the present concepts concerning the pathogenesis and differential diagnosis of this disorder, and the results of treatment with cortisone and some of the newer closely related steroids.

TABLE 1.—*The Incidence of Sex and Type and by Treatment and Mortality of the Eighty-Seven Patients with Adrenal Hyperplasia Seen at the Harriet Lane Home*

	Incidence by Sex and Type			
	Virilism Alone	Na Losing	Hypertension	Total
Females	41 *	24	3	68
Males	11	6	2	19
Total	52	30	5	87

	Incidence by Treatment and Mortality					
	Treated with Cortisone		Untreated		Total	
	Alive	Dead	Alive	Dead	Alive	Dead †
Females	56	3	5	3	61	6
Males	15	1	3	1	18	2
Total	71	4	8	4	79	8
	75		12		87	

* 7 raised as males.
† 6 manifested na-losing symptoms.

As shown in Table 1, of 87 patients observed 68, or 78%, were female pseudohermaphrodites. It is probable that this does not represent the true sex distribution, as the diagnosis is made more readily in females, while males often die in infancy from salt loss before the true nature of the disorder is suspected. Thirty, or approximately one-third, of the patients had associated salt-losing symptomatology. Seventy-five patients have been treated, of whom only four have died, so that the mortality was 5.3% in this group in contrast to 33% in the untreated patients. Table 2 shows the duration of continuous therapy to the present date.

Pathogenesis

Perfusion of animal adrenals with C^{14}-labeled acetate and cholesterol [14] and studies of urinary steroids in normal persons and in patients with adrenal hyperplasia have

TABLE 2.—*Duration of Continuous Treatment with Cortisone or "Cortisone-like" Steroids*

Yr.	Males	Females	Total
Over 7		1	1
6-7		7	7
5-6	5	5	10
4-5	3	11	14
3-4	5	12	17
2-3	1	13	14
1-2	1	5	6
<1	1	5	6

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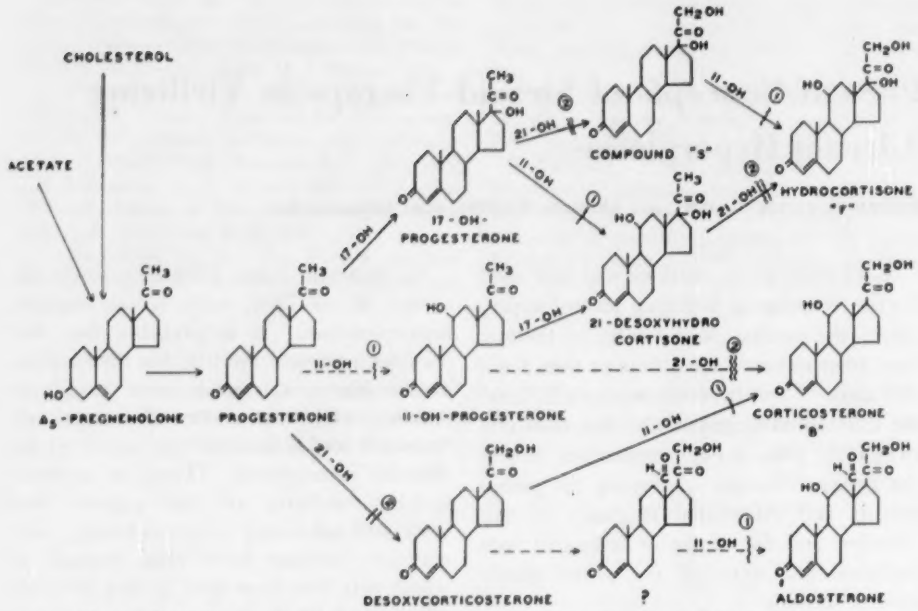

Fig. 1.—This diagram shows one concept of the metabolic pathways of synthesis of 21-carbon adrenal steroids from acetate and cholesterol; (*1*) represents the block of hydroxylation of the 11-carbon atom which is present in the hypertensive type of virilizing adrenal hyperplasia; (*2*) represents the defective hydroxylation of the 21-carbon atom which is thought to be present in a majority of patients with this syndrome not of the hypertensive type.

established in part the normal pathways of biosynthesis of adrenal steroids and the defects which may be responsible for the virilizing syndrome.[15-17] Dorfman,[18,19] Jailer et al.,[20] and others [21] postulated that there was a partial defect in the ability of the abnormal adrenal to convert progesterone to hydrocortisone and that abnormal virilizing steroids were formed instead. In attempting to maintain an adequate supply of hydrocortisone there was postulated a compensatory increase in the secretion of the adrenocorticotropic hormone, and an elevation subsequently was demonstrated.[22] As shown in Figure 1, Jailer et al. and others implicated a defect of hydroxylation at the 21-carbon in some patients. Subsequently, in patients with the hypertensive type of virilizing adrenal hyperplasia Eberlein and Bongrovanni [23] demonstrated defective hydroxylation of the 11-carbon atom, resulting in excessive production of desoxycorticosterone and compound S. The explanation for the tendency of some patients to lose sodium and retain potassium is not clear. It has been suggested that such patients secrete a "salt-losing" steroid or a pattern of steroids inhibiting sodium reabsorption, but this has never been demonstrated. Prader has recently presented data suggesting that some patients without salt-losing symptomatology and infants recovered from the salt-losing tendency have elevated aldosterone levels, which he has interpreted as a compensation for a "salt-losing hormone." [24] On the other hand the possibility that the "salt losers" have defective aldosterone secretion has not been excluded, and preliminary studies done in conjunction with Dr. Grant Liddle, measuring aldosterone excretion in our untreated patients with this complication, are somewhat suggestive of this. These results will be the basis for a subsequent report.

Differential Diagnosis

As pointed out in previous publications the differentiation of the adrenogenital syn-

TABLE 3.—*The 17-Ketosteroid Excretion of Untreated Patients with Adrenal Hyperplasia According to Age*

Age	No. Patients	17-Ketosteroids, Mg. In Patients	Normal Value
0-6 mo.	19	1-10	<0.5
7-12 mo.	3	3-10	<0.5
1-5 yr.	26	4-30	<1.0
6-9 yr.	9	11-40	<2.0
10-15 yr.	6	16-50	<10.0
> 15 yr.	12	21-80	<15.0

drome from other forms of pseudo- or true hermaphroditism or from other types of male sexual precocity depends upon the demonstration of excessive amounts of urinary 17-ketosteroids. The values which we have observed in different age groups are shown in Table 3. It is worthy of emphasis that during the first two weeks of life the normal newborn baby may have an elevated ketosteroid excretion.[25] Accordingly the test should be repeated after this time.

When an increased excretion of 17-ketosteroids is found, it is necessary to exclude the presence of a virilizing tumor instead of hyperplasia by demonstrating that cortisone causes definite suppression of the 17-ketosteroid output. Figure 2 shows the suppression of urinary 17-ketosteroids in a patient with adrenal hyperplasia and lack of suppression in a patient with a virilizing tumor. This observation has been confirmed by others.[26,27]

Patients with the adrenogenital syndrome show an accelerated rate of osseous development. Figure 3 illustrates the findings in our patients. This is not diagnostic, however, as similar acceleration is observed in all types of sexual precocity.

Determination of the sex chromatin pattern also is of value, as the finding of a male chromatin pattern in an infant with ambiguous genitalia precludes the diagnosis of female pseudohermaphroditism due to adrenal hyperplasia. This test should be performed especially in persons with this syndrome who appear to be cryptorchid males, as occasionally in female pseudohermaphrodites labial fusion is so complete as to form a scrotal-like sac and a phallic urethra. If such a patient is to be reared as a male, a panhysterectomy and oophorectomy are indicated.

Method of Treatment

Virilizing Adrenal Hyperplasia Without Salt-Losing Symptomatology.—The majority of patients have been treated with cortisone or hydrocortisone. In our experience there is essentially no difference in the effective dosage of these two steroids. Intramuscular cortisone produces superior results in most instances because of its slow absorption over a two- to three-day period, but oral medication also can be utilized satisfactorily. Table 4 has been adapted from previous publications,[8,9] and shows the average initial and maintenance doses.[8,9]

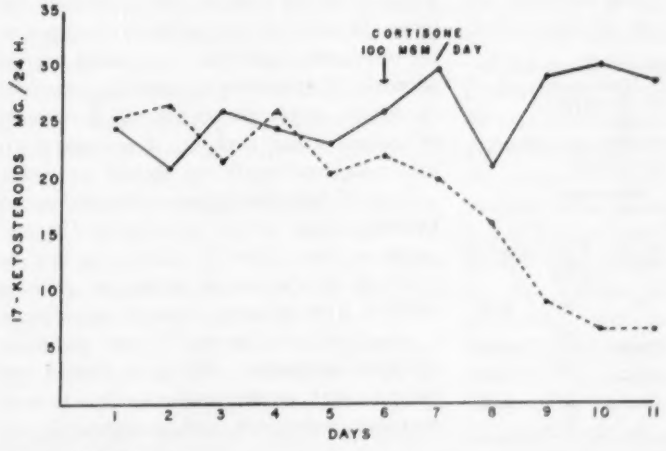

Fig. 2.—Differentiation of virilizing adrenal hyperplasia and virilizing tumor by response of 17-ketosteroid excretion to cortisone. The solid line represents the failure of a patient with a virilizing tumor to respond to cortisone. The dotted line represents the response of the patient with adrenal hyperplasia.

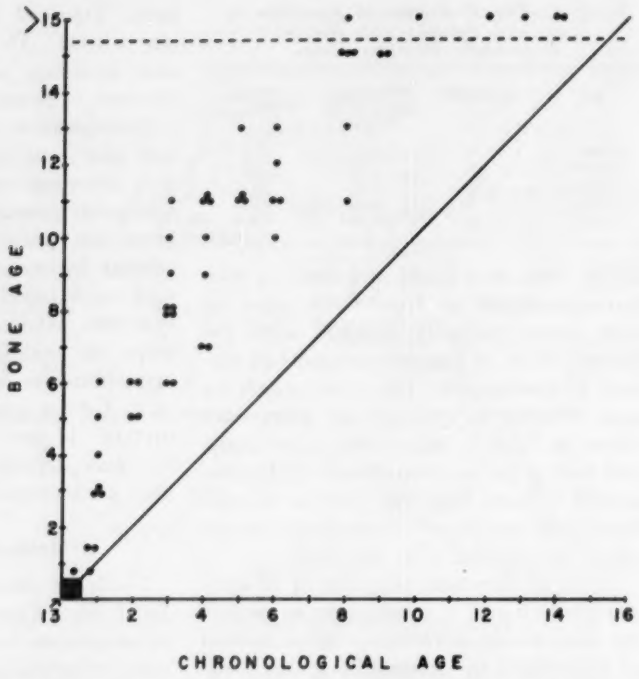

Fig. 3.—Bone age before therapy. This graph presents the advanced bone age of untreated patients with adrenal hyperplasia. It is noteworthy that only 1 of 14 patients had an advanced bone age in the first six months of life.

It is important to realize that when cortisone is given orally approximately two to three times the daily intramuscular dose is required and that this must be given in divided doses, preferably three or four times daily, as the biological half-life of oral cortisone is approximately two hours. Even when oral cortisone is to be used for maintenance we prefer to accomplish the initial suppression of the adrenal by giving cortisone intramuscularly for a 5- to 10-day period.

TABLE 4.—*Dosage of Cortisone Necessary for Initial Suppression and Maintenance of Patients with Adrenal Hyperplasia According to Age*

Age, Yr.	Dose of Cortisone, Mg.				
	Initial I.M.	Maintenance			
		I.M.		Oral	
		Amount/3 Days	Amount/Day	B.I.D. or T.I.D.	Amount/Day
Over 6	100 Q.D.	75	25	25	50-75
2-6	50 Q.D.	50 or 75	16-25	12.5 or 25	37.5-50
Under 2	25 Q.D.	25 or 37.5	8-12	5 or 10	15-20

In regulating the maintenance dosage of cortisone in growing children it is advisable to follow the rates of growth and osseous development in addition to the 17-ketosteroid excretion, as shown in Figure 4. It is important to explain to the parents and attending physician that when a patient is receiving suppressive doses of cortisone surgical operations, severe acute infections, and other forms of stress present special hazards because the adrenals are unable to respond to the increased requirements as would normal adrenals. Preparatory to surgical operations or during severe illness increased amounts of intramuscular, oral, or, if necessary, intravenous hydrocortisone should be given.

Segaloff has used aqueous suspensions of hydrocortisone acetate weekly in 250 mg. intramuscular doses.[28] Although this is probably satisfactory in adults, in growing children it would seem advisable to maintain a more uniform metabolic state by more frequent medication. We have treated two patients with an intramuscular injection of cortisone oenanthate and caprylate in oil,

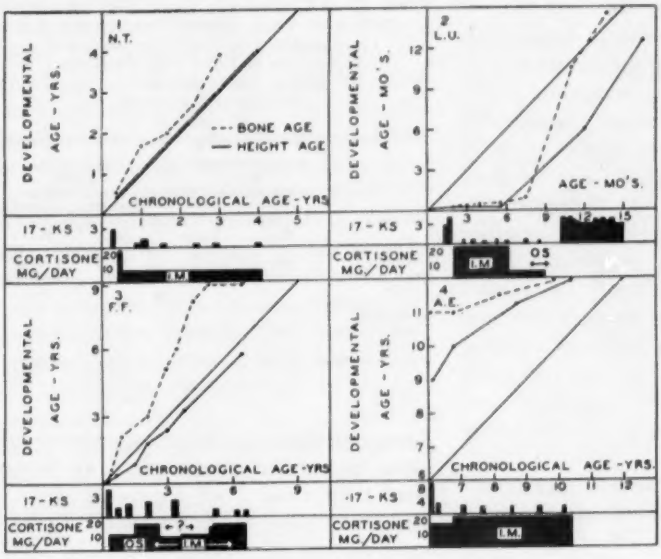

Fig. 4.—This series of charts plots the height age and bone age versus the developmental age of patients under therapy. Case 1 demonstrates adequate treatment with normal growth. Case 2 represents the plateauing of growth that occurs with excessive therapy. Case 3 demonstrates poor treatment, with resulting rapid skeletal maturation. Case 4 represents how height may be permitted to "catch up" with skeletal maturation in older children under therapy.

believed to be utilized at a slow rate. One 12-year-old boy has required 750 mg. intramuscularly every two weeks for the past 18 months to suppress the 17-ketosteroid excretion to normal levels, and a 23-year-old woman maintained on 250 mg. every 2 weeks eventually escaped suppression and was then given prednisone (Meticorten).

Prednisone has been successfully used in seven patients age 4 to 23 years at doses of 5 to 15 mg. per day (2.5 to 5.0 mg. b. i. d. or t. i. d.). In our experience prednisone is five times as potent as oral cortisone in suppressing elevated 17-ketosteroids, although Kupperman et al. found it only three times as potent in acute experiments.[29]

Virilizing Adrenal Hyperplasia with Salt-Losing Symptomatology.—Treatment of patients with an associated defect of electrolyte regulation is difficult. When an infant is in a dehydrated state isotonic sodium chloride or salt should be given in equivalents of 4 to 8 gm. during the first 24 hours, followed by maintenance doses of 2 to 6 gm. of salt added to the diet daily. Desoxycorticosterone (Doca) acetate is also given immediately and daily thereafter in doses of 1 to 4 mg., utilizing body weight, clinical hydration, and serum electrolytes as guides to therapy. After establishment of dosage requirements desoxycorticosterone acetate pellets are implanted. In our experience two to five 125 mg. pellets have been required, depending on the severity of the salt-losing tendency. Only 2 patients of the 30 in this group did not require desoxycorticosterone acetate or other salt-retaining steroids.

Cortisone should be started as soon as two or three 24-hour urine collections for 17-ketosteroids have been collected to confirm the diagnosis. Treatment with cortisone is identical for patients with and without salt-losing symptomatology.

Two synthetic halogenated steroids, fludrocortisone (9α-fluorohydrocortisone) and 9α-chlorohydrocortisone, designed to supply both the adrenal suppressing effect and the sodium-retaining effect, have been under investigation. Six patients age 2 months to 5 years have been given prolonged trials with fludrocortisone. Dosages of 0.5 mg. per day without salt supplement invariably produced hypertension after periods varying from 7 to 15 months and inadequately suppressed 17-ketosteroid excretion and growth. Suppressive effect of this compound is only 10 times that of cortisone, and the salt-

retaining effect is five to six times that of desoxycorticosterone acetate. Kupperman et al. reported essentially the same suppressive effect and found this compound inadequate to maintain adrenal suppression without producing either hypertension or edema.[29] Goldfien et al. in acute experiments found 1 mg. of fludrocortisone equivalent to 4 mg. of desoxycorticosterone acetate, which may be a conservative figure as compared with our studies.[30] Preliminary data indicate that smaller doses in the range of 0.1 to 0.2 mg. for infants and children, supplemented with cortisone, may adequately suppress 17-ketosteroid excretion and growth without producing adverse symptoms.

Our experience with 9α-chlorohydrocortisone in five patients aged 1 month to 5 years has been encouraging, as a dosage of 5 mg. given orally once a day has controlled androgenic manifestations and maintained normal electrolytes without producing hypertension or edema when used over a period as long as 18 months.

It has been reported previously that there is a tendency for these patients to recover from their salt-losing manifestations.[8,9] Of 20 patients in whom desoxycorticosterone acetate pellets were implanted or one of the other sodium-retaining steroids were utilized 12 have not required additional pellets and have required no other sodium-retaining steroids for periods of one to seven years; nevertheless, several of these patients subjected to very low-salt diets did manifest dehydration and inability to retain salt. It is to be noted, however, that these manifestations occurred only with severe deprivation. Three patients still require sodium-retaining steroids at age 5 years, but these are exceptional in this respect.

The various adrenal-suppressing and salt-retaining properties of the compounds used are compared in Table 5.

TABLE 5.—*A Comparison of the Various Steroids in Relation to Their Adrenal-Suppressing Action (as Compared to Oral Cortisone) and in Relation to Their Salt-Retaining Action (as Compared to Desoxycorticosterone Acetate)*

	Adrenal-Suppressing Action (Compared to "E")		Salt-Retaining Action (Compared to Desoxycorticosterone)	
	Mg.	Factor	Mg.	Factor
Cortisone	100	1	200	0.005×
Prednisone	20	5×	350	0.003×
Desoxy corticosterone	----	----	1	1
9α-Fluoro-hydrocortisone	10	10×	0.15–0.2	5–6×
9α-Chloro-hydrocortisone	20–25	4–5×	2.5	0.4×

Results of Treatment

When adequate treatment is begun in infancy normal growth occurs, as illustrated in Case 1 of Figure 4. Excessive cortisone therapy produces a Cushing appearance and plateauing of the growth curve, as demonstrated by Case 2 of Figure 4. Case 3 represents poor treatment, with resulting rapid skeletal maturation.

When older children are treated before fusion of the epiphyses has occurred excessive virilization is inhibited and accelerated epiphyseal ossification is checked, while growth in height may continue, as shown by Case 4 of Figure 4. This permits the attainment of a greater height than would occur without treatment. When children are not treated before there is far-advanced skeletal development early epiphyseal fusion causes them to be short.

Sexual development in both the male and the female child occurs along normal patterns when therapy is adequate. In the male maturation of the testes occurs, and in the female all the manifestations of estrogen production appear coincident with an adolescent bone age—i. e., 11 to 15 years—rather than with chronological age.

Ten adult female patients between the ages of 18 and 48 years have been treated. With two exceptions these patients had not shown any development of secondary sex characteristics or estrogen manifestation. It is of interest that before treatment one of these patients in whom the diagnosis was confirmed by exploratory operation and by suppression of the 17-ketosteroid excretion by cortisone had menstruated before she had

become markedly virilized. Three of these patients are married and carry on a normal marital life. One of our patients has conceived and is in the third month of pregnancy, and two patients have been reported elsewhere to have given birth to normal children. It is noteworthy that these older patients often have bizarre physical and psychological complaints for the first four to eight weeks after therapy is begun. For example, one patient complained of vague tiredness and/or depression and the sensation of having a full bloated stomach, while simultaneously the appetite was insatiable. It is important, as pointed out by Money, Hampson, and Hampson, that the physician realize the symptoms are induced by the steroid or the altered metabolic state and not neurotic in origin.[31]

Hirsutism, one of the major problems in patients not treated early, usually decreases gradually. Only a few female patients who were required to shave before treatment were able to dispense completely with this unpleasant reminder of their virilization, although this was required much less frequently. Hair over the body as well as on the face became much less coarse and lighter in color. Baldness also has been an occasional accompanying finding, and partial regrowth of hair has occurred with the use of cortisone. Under treatment feminine contours replaced Herculean builds. An example of what may be accomplished with treatment in the adult female is portrayed in Figure 5.

At times female pseudohermaphrodites are encountered who have been reared as males because of mistaken diagnoses. Likewise before the advent of cortisone therapy progressive virilism was so inevitable that it was decided at times to rear these patients as boys and to carry out the plastic construction of a penile urethra and scrotum. Money, Hampson, and Hampson have shown that in these persons it is hazardous to alter the sex of rearing after the age of about 2 or 3 years and that they adjust completely to their adopted sex.[32] During childhood it is desirable to give these patients cortisone to prevent early virilization, excessive growth, and premature epiphysial fusion. It is important, however, to have oophorectomies and hysterectomies performed to prevent feminization with breast development and menstruation which would follow cortisone therapy. Seven of our female pseudohermaphrodites reared as males have had these operations. After growth has ceased and the patient has reached the usual age of puberty cortisone may be discontinued and the patient allowed to virilize under the influence of adrenal androgens.

Fortunately improvement in early diagnosis through measurement of the 17-ketosteroid excretion and determination of the sex chromatin pattern and the use of cortisone in treatment should eliminate the necessity of rearing the female pseudohermaphrodite as a male. When the clitoris is conspicuously enlarged it has been our custom to have clitorectomy performed within the first year or two of life, provided a salt-losing tendency is absent or has been thoroughly controlled. Separation of the labial fusion can be carried out simultaneously, or at a later date if clitorectomy is not indicated.

In a young male with adrenal hyperplasia cortisone therapy is indicated principally to prevent premature epiphyseal fusion and to delay precocious virilism and excessive growth which would make the patient conspicuous among his agemates. Without treatment the testes usually remain small and immature, owing to inhibition of pituitary gonadotropins by adrenal androgen, although we have seen several exceptions to this rule. Under treatment, when a patient's bone age has reached 12 to 14 years his testes will mature so that the Leydig cells will secrete androgen and the tubules develop spermatogenesis. Under the influence of testicular androgen male secondary sexual development will then progress, and eventually statural growth will cease. After this the only reason for continuing cortisone therapy would be to maintain fertility. It

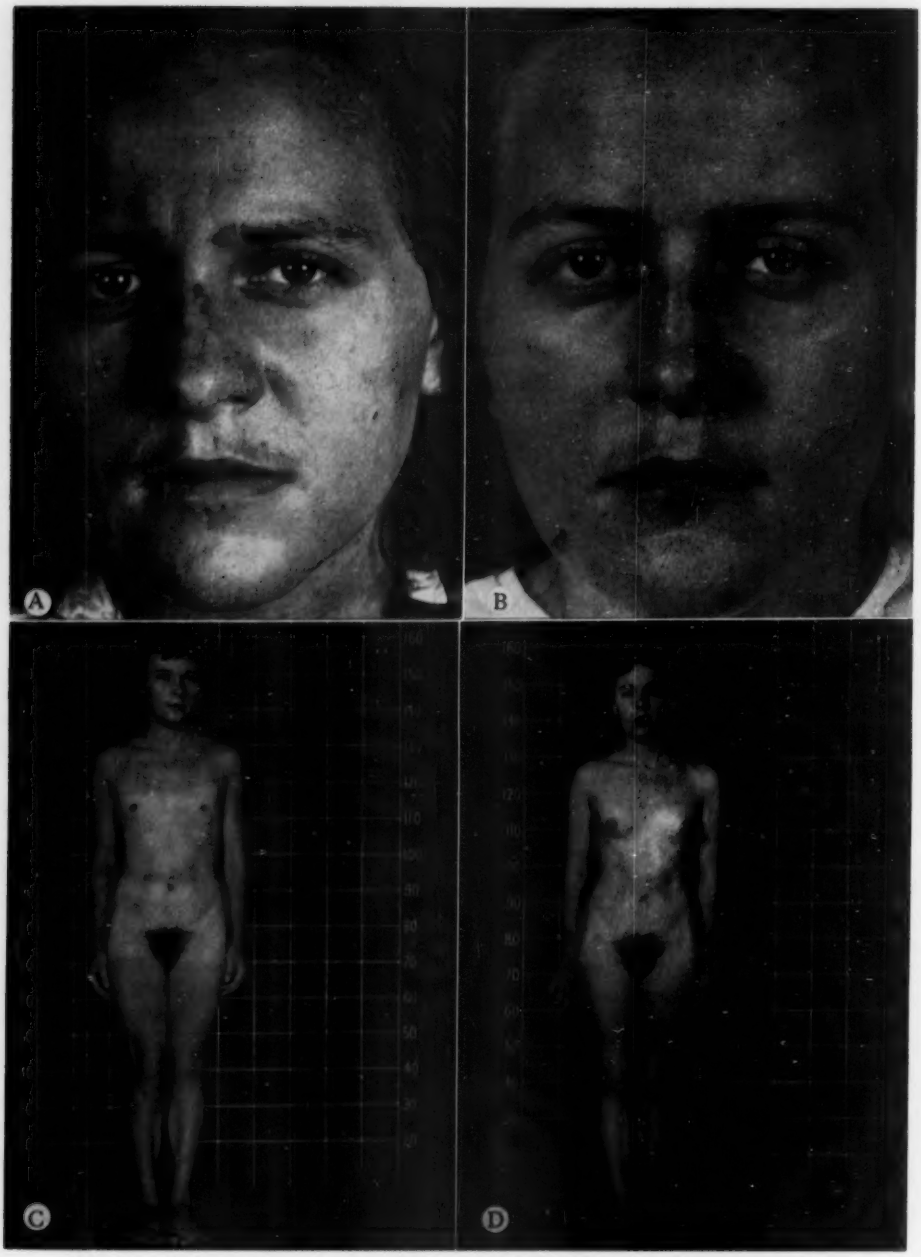

Fig. 5.—*A*, before therapy. *B*, after six months of therapy. The improvement in skin texture and complexion is shown in this adult patient six months after therapy was initiated. *C*, before therapy. *D*, after six months of therapy. The development of breasts and feminine body contours are demonstrated in this 18-year-old woman six months after therapy was begun.

has not yet been demonstrated whether withdrawal of treatment resulting in renewed secretion of adrenal androgen will inhibit spermatogenesis which has once been established. Further study of this subject is desirable.

Psychological orientation of the parents and patients as to the etiology of the condition is as important an aspect of treatment as is medical therapy. It has routinely been the policy to explain to the parents, and the patient when old enough, how adrenal hormones can produce embryological enlargement of the phallus and labial fusion in an otherwise normal female infant and how these hormones can produce virilization in an older child. With the benefit of these explanations these patients have been relieved of wondering if they are of mixed sex.

Summary

There are three types of virilizing adrenal hyperplasia: (1) virilization with salt-losing symptomatology, (2) virilization with hypertension, (3) virilization without other manifestations. These individual types are attributed to deficiencies of various enzymes necessary for synthesis of acetate and cholesterol to hydrocortisone. Adrenal hyperplasia and excessive virilization result although relative hydrocortisone deficiency exists.

Eighty-seven patients with virilizing adrenal hyperplasia have been observed. Since 1950, when Wilkins et al. introduced successful treatment by using cortisone to suppress the hyperplastic adrenal, 75 of these have been treated in our clinic. Effect of treatment has been analyzed and reported in 65 children and 10 adult females.

Treatment as proposed by Wilkins et al. initially, utilizing cortisone, and desoxycorticosterone and salt when indicated, remains the treatment of choice, although prednisone (Meticorten), depot cortisone, fludrocortisone (9α-fluorohydrocortisone), and 9α-cholorhydrocortisone also have been utilized. Experience with all these compounds is discussed.

Adequate therapy as measured by suppression of urinary 17-ketosteroid excretion, inhibition of virilization, and restoration of normal physical and skeletal growth has permitted these patients to develop as normal children and adults. These aspects are discussed in detail.

The Johns Hopkins Hospital.

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The Effects of Estrogens on Serum Lipids in Women

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In 1949 Eilert demonstrated the lipid-shifting effects of estrogens in postmenopausal and castrated women.[1] Because of the preponderance of men suffering from coronary heart disease in middle age the relationship between the lipid effects of estrogens and coronary atherosclerosis has been studied chiefly in men. Recently several groups have clearly documented the striking effects of estrogens on the serum lipids of men with coronary heart disease when employed in adequate dosage for sufficient time.[2-6] However, since there is an increased incidence of coronary heart disease in postmenopausal women, the growth of the aging population has resulted in an increasingly important number of women suffering from this disease.

The rise of serum cholesterol levels in women with advancing age has been well established,[7-9] but the reasons for this remain obscure. The physiological decrease of ovarian function as reflected by the progressive fall of urinary estrogen levels in aging women [10] offers one of several possible explanations. Furthermore, observations of cyclic changes of the serum lipids in young women, correlated with estrogenic activity in the menstrual cycle,[11] suggest a direct relationship between serum lipids and estrogen metabolism. Additional positive evidence is the fact that the serum lipids of both men and women respond promptly to estrogen administration and return to pretreatment levels when estrogen is omitted. If it were possible to demonstrate the development of abnormalities in the serum lipids of women bilaterally oophorectomized prior to the menopause the case for such a relationship would be further strengthened.

Pathologic studies of bilaterally oophorectomized women at autopsy have demonstrated increased coronary atherosclerosis.[12] Additional pathologic studies of hyperestrogenic and hypoestrogenic clinical states have shown a clear relationship between estrogen levels and the degree of coronary atherosclerosis.[13] Recent clinical studies in our laboratory of oophorectomized women have lent support to this concept.

The studies to be presented demonstrate that castration of women prior to the menopause results in the development of prematurely abnormal serum lipid levels and that in such persons developing coronary heart disease these abnormalities are more profound. The prompt reversal of these lipid abnormalities as a result of estrogen therapy suggests a reasonable approach to the problem of the treatment of coronary heart disease in women.

Materials and Methods

One hundred eighty-eight clinically normal women, ranging in age from 21 to 70 years, were selected from various departments of The Memorial Hospital. These included nurses, technicians, secretaries, volunteer workers, and other employees. Patients who underwent bilateral oophorectomy prior to age 45 at The Memorial Hospital during the 20-year period 1936 to 1955 are being traced. To date, 107 of these persons have been contacted without selection, and all have undergone clinical

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From the Medical Division and the Research Laboratory of The Memorial Hospital.

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Read in the Symposium on the Use of Androgens and Estrogens and Their Metabolic Effects before the Joint Meeting of the Section on Experimental Medicine and Therapeutics and the Section on Internal Medicine at the 106th Annual Meeting of the American Medical Association, New York, June 6, 1957.

TABLE 1.—*Serum Lipid Values of 188 Clinically Normal Women in Various Age Groups* *

Age, Yr.	No. Women	Cholesterol, Mean ± S.E.M., Mg./100 Ml.	Phospholipid, Mean ± S.E.M., Mg./100 Ml.	C/P Ratio, Mean ± S.E.M.	β-/α-Lipoprotein Cholesterol Ratio, Mean ± S.E.M.
21-30	53	187 ± 4.3	175 ± 4.0	1.07 ± 0.023	2.3 ± 0.15
31-40	59	214 ± 5.0	186 ± 4.8	1.16 ± 0.017	2.7 ± 0.13
41-50	53	235 ± 5.3	198 ± 4.6	1.20 ± 0.022	2.8 ± 0.15
51-70	23	262 ± 7.9	218 ± 7.4	1.21 ± 0.027	3.2 ± 0.21

* S.E.M. indicates standard error of the mean.

and laboratory evaluation. The last group studied included 74 women with coronary heart disease who were seen in private practice.

Serum cholesterol and phospholipids were determined by methods previously described.[5] It should be noted that the phospholipid determinations employed purification of the crude lipid extract by reextraction into petroleum ether, resulting in lower phospholipid values and hence relatively higher cholesterol-phospholipid (C/P) ratios than those reported by others. Separation of the α- and β-lipoprotein fractions of serum was accomplished in earlier studies by electrophoresis in filter paper[5] and more recently by ultracentrifugal flotation of the β-lipoproteins.[14] Replicate separations of the lipoproteins of the same sera by both methods yielded a product-moment correlation coefficient of +0.82. After separation the cholesterol content of both fractions was determined. The C/P and β- to α-lipoprotein cholesterol ratios were derived from these results.

Results and Comment

Table 1 shows the alterations in serum lipids with increasing age in clinically normal women aged 21 to 70. There is a more striking rise in serum total cholesterol than in phospholipids, resulting in an increase of the C/P ratio associated with aging. The cholesterol data are very similar to those reported by Jones et al.,[7] Dawber,[9] and Lawry et al.[8] The β- to α-lipoprotein cholesterol ratio also increases gradually with age. This correlates well with the increase of the low-density lipoproteins (S_f 12-20 and S_f 20-100) described by other investigators.[7,8] The above gradual changes raise the question of whether factors other than the cessation of ovarian estrogen production at the menopause should be considered in explanation. The effect of weight gain, commonly noted with aging, is now being investigated, both from the points of view of "fatness" (stable but abnormally high body weight) and of "fattening" (continuing yearly increase of weight).

In the Figure the serum cholesterol, C/P ratios, and β- to α-lipoprotein cholesterol ratios of normal women, tabulated in Table 1, are compared with the corresponding lipid measurements from 107 persons aged 31 to 70 who had been suddenly deprived of ovarian estrogens by oophorectomy prior to age 45. It is notable that the serum cholesterol and the β- to α-lipoprotein cholesterol ratio are significantly higher in the oophorectomized women in all age groups. However, the apparent elevation of the C/P ratio in the castrated group was not significant, the increase of serum cholesterol

Comparative serum lipid values in clinically normal versus bilaterally oophorectomized women in various age groups. *N* indicates number of persons; N. S., not statistically significant, $P>0.05$. Brackets enclose ± one standard error.

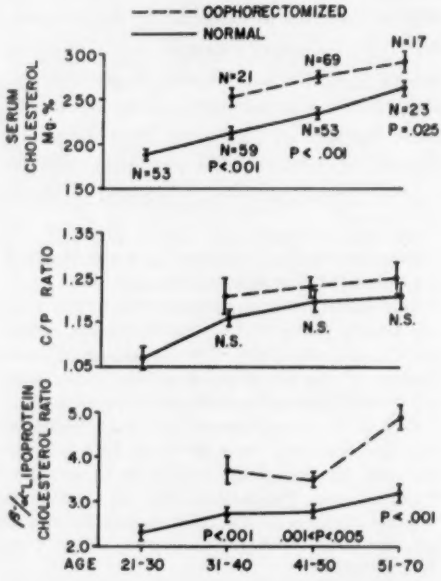

TABLE 2.—*Differences in Serum Lipid Values Between Oophorectomized Patients With Coronary Heart Disease and Age-Matched Oophorectomized Women Without Disease* *

Group	Av. Age, Yr.	No. of Women	Cholesterol, Mean ± S.E.M., Mg./100 Ml.	Phospholipids, Mean ± S.E.M., Mg./100 Ml.	C/P Ratio, Mean ± S.E.M.	β-/α-Lipoprotein Cholesterol Ratio, Mean ± S.E.M.
Coronary	52.5	39	276 ± 6.3	224 ± 5.2	1.24 ± 0.022	4.2 ± 0.21
No disease	52.2	39	268 ± 7.6	230 ± 6.1	1.17 ± 0.019	3.6 ± 0.18
Statistical Significance			N.S.	N.S.	$0.01 < P < 0.025$	$0.01 < P < 0.025$

* S.E.M. indicates standard error of the mean; N.S., not statistically significant.

being nearly matched by an increase of phospholipids. The most abnormal finding in the castrated group was the increase of the β- to α-lipoprotein cholesterol ratio in the older women oophorectomized prior to the natural menopause. These differences are ascribed to the loss of ovarian estrogen in the castrated group.

Table 2 compares the serum lipids of 39 oophorectomized patients suffering from coronary heart disease with those of age-matched clinically normal women who were also oophorectomized. Although the increase of serum cholesterol and the decrease of phospholipids in the former group were not significant, the resultant C/P ratio was significantly elevated, as was the β- to α-lipoprotein cholesterol ratio in the coronary group. However, the predictive value of the serum lipid changes in individual patients was low, since 49% of the coronary patients showed C/P ratios below the 75th percentile of the normal group, and 56% had β- to α-lipoprotein cholesterol ratios below this 75% cutting point. Similar overlapping of serum lipid results between normal and coronary groups was observed in men in a recent study by Lawry et al.[8]

At the present time the explanation for the differences of the serum lipid values between the clinically normal oophorectomized and coronary oophorectomized subjects is unclear. Since it has been shown by Marmorston et al.[15] that postmenopausal women with myocardial infarction excrete less total urinary estrogens, measured by a bioassay method, than do normal postmenopausal women, it is possible that abnormal extra-ovarian estrogen metabolism may be responsible for altered serum lipids and hence atherosclerosis in certain oophorectomized persons. Studies with isotopically labeled estrogens to delineate the nature of these abnormalities, if any, are being undertaken in our laboratory.

The availability of an adequate number of female patients with coronary heart disease made possible an evaluation of both the clinical and serum lipid effects of estrogen on these subjects. Table 3 summarizes the pertinent clinical features of a group of 35 previously hysterectomized patients. Of these, 11 had undergone both hysterectomy and oophorectomy prior to age 45. Hypertension was a frequent finding. Myocardial infarction had occurred in almost half of the patients. Diabetes was present in only one person. There were two deaths during therapy, one occurring shortly after treatment was started and one after 17 months.

Table 4 depicts the response of the serum lipids after three months of giving 5 or 10 mg. of conjugated estrogenic substances (Premarin) to 30 of these patients. This dosage range was selected because it had been found in a previous study to cause rapid significant alterations of the serum lipids in male coronary patients[5] and be-

TABLE 3.—*Clinical Data on Women with Coronary Heart Disease Treated with Five to Ten Milligrams of Conjugated Estrogenic Substances (Premarin) Daily*

	No.	Per Cent
Patients studied	35	
Average age	55 yr. (42-65)	
Average duration of treatment	14 mo. (2-31 mo.)	
Oophorectomized prior to age 45	11	31
Hypertension (B.P.>150/100)	25	71
Borderline hypertension (140/90<B.P.<150/100)	5	14
Type of disease		
Angina pectoris (only)	21	60
Myocardial infarct	14	40
Diabetes	1	
Deaths during therapy	2	
One after 17 mo.		
The other after 2 mo.		

TABLE 4.—*Response of Serum Lipids to Five to Ten Milligrams of Conjugated Estrogenic Substances (Premarin) Daily in Thirty Women with Coronary Heart Disease*

	Cholesterol, Mg./100 Ml.	Phospholipids, Mg./100 Ml.	C/P Ratio	β-/α-Lipoprotein Cholesterol Ratio
Control level	266 ± 9.6	222 ± 8.1	1.21 ± 0.027	4.2 ± 0.27
Change from control	−28 ± 7.8	+36 ± 6.6	−0.29 ± 0.032	−35 ± 5.0%
3 mo. therapy (Level achieved)	(238)	(258)	(0.92)	(2.7)
Significance of change	t=3.59 $0.001<P<0.005$	t=5.46 $P<0.001$	t=9.06 $P<0.001$	t=7.00 $P<0.001$

cause uterine bleeding was no problem in these hysterectomized patients. The effects on the serum lipids are tabulated as the mean changes from each person's control values. The average absolute levels reached are shown in parentheses. All of the changes were statistically highly significant, with P values less than 0.005 for cholesterol and less than 0.001 for the other measures. The dramatic decrease of the C/P ratio, from 1.21 to 0.92, was due to both a decrease of cholesterol and a marked increase of phospholipids. The 35% decrease of the β- to α-lipoprotein cholesterol ratio, from 4.2 to 2.7, was due not only to an absolute decrease in the β-lipoprotein fraction but also to an increase in the α-fraction. The role of these two distinct lipoprotein moieties in atherogenesis is currently under intensive study in several laboratories. The mechanisms of the reciprocal changes of the serum cholesterol and phospholipids and of the α- and β-lipoprotein fractions resulting from estrogen administration will be studied in our laboratory.

In the male patients previously studied the chief side-effect of estrogen therapy was feminization, including gynecomastia and testicular atrophy. In contrast, the feminizing side-effects of estrogen were found to be clinically desirable in the women patients of the present study. The only unfavorable side-effects were the return of migraine and the development of nocturnal leg-muscle cramps in a few patients.

Summary and Conclusions

Although the serum lipids, including total cholesterol, phospholipids, cholesterol-phospholipid (C/P) ratio, and β- to α-lipoprotein cholesterol ratio, increase with age in normal women, these increases are more prominent in women oophorectomized prior to the menopause.

The serum lipids of 39 oophorectomized patients with coronary heart disease were "worse" than those of age-matched clinically normal women who were also castrated. However, little predictive value could be assigned to these serum lipid changes because of considerable overlapping between the groups.

The prompt response of the serum lipids and the minimal unfavorable side-effects in hysterectomized patients with coronary disease treated with estrogen suggest a logical therapeutic approach to coronary heart disease in these women.

Miss Patricia Marsaw, Miss Anne E. Murphy, Mrs. Katherine S. Marsella, and Mr. Raoul J. LeBeau provided technical assistance. Ayerst, McKenna, and Harrison, Ltd. supplied the Premarin used in this study.

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Experimental Basis for Anabolic Therapy

GILBERT S. GORDAN, M.D., Ph.D., San Francisco

Currently, chemical analogs of the naturally occurring hormones are being prepared and studied in large quantities in the hope of finding useful therapeutic agents. The recent demonstration that naturally occurring hormones that were once thought to be single are really complexes of metabolically active substances has multiplied the number of known hormones remarkably. For example, in the case of the thyroid hormones we now know that thyroxin is but one of a large complex of chemically related substances and that some of its metabolites are, in fact, more potent than thyroxin itself. There is also some indication that the degradation products may be different, not only quantitatively but also qualitatively, in their metabolic actions. For example, triiodothyropropionic acid, which may be looked upon as a deiodinated, deaminated analogue of thyroxin, has only 15% of the ability of *l*-thyroxin to increase oxygen consumption and only one-quarter of its ability to suppress the uptake of radioiodine but is 300 times as effective in producing metamorphosis of tadpoles.[1] The generalization that chemical modifications may result in major alteration of the action of the hormone is perhaps best known from the considerable clinical and laboratory experience obtained with synthetic adrenal cortical steroids. One of the most familiar examples is fludrocortisone (9α-fluorohydrocortisone), where the introduction of a fluorine atom in the nine position has not only quantitatively increased the efficacy of the agent but has disproportionately increased its actions upon sodium and potassium metabolism. Thus, this agent is many times as effective as hydrocortisone in suppressing adrenocortical activity and in relieving the clinical manifestations of rheumatoid arthritis, but it has limited therapeutic usefulness for either of these purposes because of its major propensity to produce serious edema. On the other hand, unsaturation of the bond between the first and second carbons of the cortisone or hydrocortisone molecule also increases antirheumatic activity, while it greatly reduces the effects on electrolyte metabolism. Thus, prednisone and prednisolone have enjoyed wide popularity because ordinary doses rarely produce edema or depletion of potassium, despite the fact that they are fully as active as cortisone or hydrocortisone in relieving rheumatoid arthritis and in producing osteoporosis, peptic ulceration, and the other effects of adrenal corticoids.

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From the Endocrine Clinic of the Department of Medicine, University of California School of Medicine, and The Langley Porter Clinic of the State Department of Mental Hygiene.

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Mrs. Frieda Smith did the chemical determinations, Miss Julia Jamison supervised dietary intake, and Dr. Harry Rudel, of Pfizer Laboratories, and Dr. C. J. O'Donovan, of The Upjohn Company, gave permission for use of some of their data. Dr. Eugene Eisenberg, Mr. Irving Shemano, and Mr. William Sakamoto assisted with the levator ani assays.

In order to obtain compounds which retain one action that may be desirable while at the same time obviating or minimizing an undesirable action it is of course essential to have adequate pharmacologic tests for the specific actions involved. Recently considerable effort and expense have gone into an attempt to separate anabolic activity from androgenicity. At the very outset, and at the risk of being anticlimactic, I might state that this separation has not been achieved to the entire satisfaction of the clinician. In part, this lack of dissociation may result from certain fundamental difficulties in the biologic assays used, and it is with the hope of clarifying these pitfalls that the following illustrative material has been assembled.

It has long been known that androgens have potent anabolic properties. The first demonstration of this action was that of the Italian clinician, Sacchi, who in 1895 described a boy 9 years 7 months old in whom precocious puberty was associated with a testicular tumor.[2] This tumor must have elaborated enormous amounts of androgen, for the young boy had the genital development and beard of an adult man. These spectacular effects were accompanied by a remarkable degree of muscular development, which this astute clinician did not fail to note, photograph, and report. The similar muscularity of young children afflicted with adrenocortical hyperplasia producing excess androgens has led to the descriptive term "infant Hercules syndrome." Despite these dramatic clinical observations the anabolic action of the male sex hormone was not established upon a firm experimental basis until 1934, when Kochakian and Murlin found that injection into normal or castrated dogs of a male hormone extract derived from medical students' urine caused a great retention of nitrogen.[3] These authors noted that the amount of nitrogen retained was far too large to be explained by the growth of genital tissues and that general tissue growth must have occurred. Very shortly after, synthetic preparations of testosterone propionate became available, and Kenyon and the group at the University of Chicago made entirely similar deductions from the retention of protoplasmic constituents produced by injection of testosterone propionate in normal and eunuchoid men.[4]

Few biologic properties have been so well documented as the anabolic action of the testosterone compounds. Therapeutically this action is useful for the production of growth; for antidoting nitrogen loss following burns, spinal transection, or administration of corticoids, and for the reversal of calcium and phosphorus loss in patients with osteoporosis.[5] In these and other therapeutic uses the application of testosterone compounds has been greatly limited by their androgenicity. Particularly in young girls, growth can rarely be obtained with doses that do not also produce masculinization. Osteoporosis, too, is primarily a disease of women, and treatment must be given for many years. Under these circumstances androgens invariably produce some degree of virilization (acne, hirsutism, alopecia, masculinization of the body habitus, and clitoral stimulation resulting in an annoying return of libido). For these reasons an intensive search has been conducted for compounds which would have the tissue-forming effects of testosterone without its androgenic capacity. The recent discovery by Raben[6] that human growth hormone prepared from pituitary glands of human subjects has anabolic activity[7] may fill the need, but the limited amount of this material which can be obtained probably will make it desirable to prepare other compounds with similar action.

The assay currently in widest use for the detection of the anabolic action of steroid and other chemical compounds is the growth of the levator ani muscle of the castrated immature male rat. In 1941 Wainman and Shipounoff recognized that the perineal complex of the rat, consisting of the levator ani, bulbocavernosus, and ischiocavernosus muscles, could be made to grow by injections of testosterone propionate.[8] In 1947 Dr. Eisenberg, then a second-year medical student,

set about to determine whether the growth of these muscles was an anabolic or an androgenic phenomenon. He was able to demonstrate that the muscle grew in the castrated rat upon injection with pituitary extracts rich in the growth factor and in the hypothyroid castrated rat treated with thyroid alone. It was thus apparent that growth of the muscle could be achieved in the absence of the gonad or of gonadal hormone, so that the weight of the muscle might be used as an index of anabolic activity. In the course of the assay androgenic activity is indicated by the weight of the seminal vesicles. These organs can be made to grow following administration of androgens (in which case the growth is primarily epithelial) or of estrogens (in which case the growth is entirely fibromuscular). By weighing the levator ani muscle and the seminal vesicles of the treated animal one can obtain a rough index of anabolic and androgenic activity of an unknown agent.

In our initial report Dr. Eisenberg and I [9] attempted to call attention to the fact that the levator ani muscle grows to a limited degree immediately following castration, whereas the seminal vesicles rapidly plateau. In Figure 1 are shown the weights of both the levator ani muscles and the seminal vesicles of 60 rats after castration. It will be observed that the seminal vesicles remain infantile, weighing only 6 to 10 mg. after castration. During the first month, however, the weight of the levator ani muscle increases fourfold before it plateaus. (Incidentally, the fact that the muscle grows in the absence of gonadal steroids is another indication that it may reflect anabolic activity.) If, however, one assays any compound during this period of spontaneous growth one may be led to the false assumption that the agent is anabolic. Accordingly, we recommended that the test be delayed until 23 days after castration. Unfortunately this warning has not been heeded. The modification of the levator ani test in widest use is that proposed by Hershberger, Shipley, and Meyer,[10] in which the animals receive the initial injection immediately after castration. In my opinion this assay has two pitfalls, into one of which we have also fallen. One pitfall is, of course, that the muscle itself is growing spontaneously during the time of assay. The second—and this is a problem which has led us astray as well—is that the seminal vesicles are often sluggish in their response to androgens. A single week's treatment with a weak androgen may be insufficient to produce significant increase in their weight. Thus the modified test is biased in favor of anabolic action and may seriously underread androgenicity. We, too, have been guilty of underestimating androgenicity and now feel that a seven-day injection period is inadequate to rule this out, regardless of whether the seminal vesicles or the ventral prostate is taken as an end-point. Thus, as Dr. Kochakian is so fond of pointing out, one can be seriously misled by using a "quickie" method where biologic response requires a prolonged period of observation.

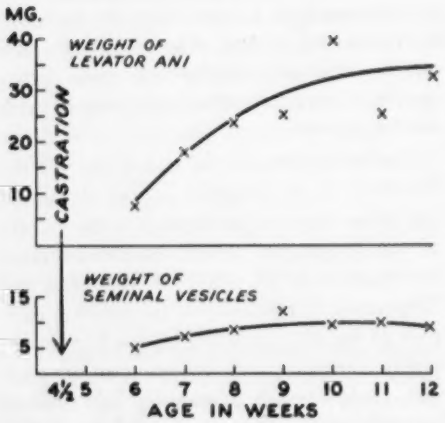

Fig. 1.—Growth of levator ani and seminal vesicles in castrated rats.

Still another difficulty arises when the period of action of the steroid does not correspond to the arbitrary seven-day test period. For example, testosterone cyclopentylpropionate was important in the seven-day test, yet when followed for 30 days it proved the most potent anabolic agent we have thus far studied (Fig. 2).[11] On the

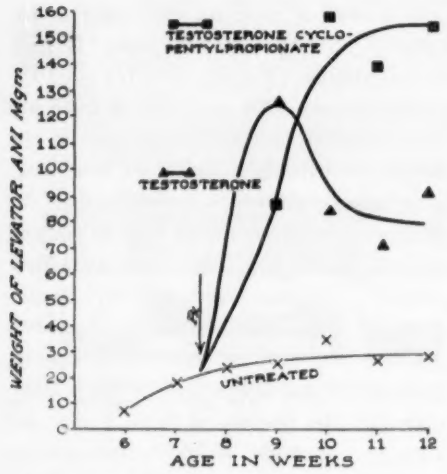

Fig. 2.—Effect of testosterone and testosterone cyclopentylpropionate upon levator ani of castrated male rats.

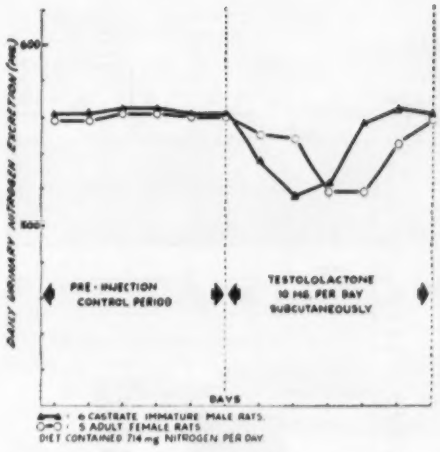
DAILY URINARY NITROGEN EXCRETION (mg)
PRE-INJECTION CONTROL PERIOD
TESTOLOLACTONE 10 MG. PER DAY SUBCUTANEOUSLY
DAYS
○ CASTRATE IMMATURE MALE RATS.
5 ADULT FEMALE RATS
DIET CONTAINED 714 mg NITROGEN PER DAY

Fig. 3.—Effect of testololactone on urinary nitrogen excretion of the rat.

other hand, testololactone (nonandrogenic steroid derivative) produces significant growth of the muscle in the standard seven-day test, but its anabolic activity is already dissipated by the end of this period, and the "rebound phase," so well described by Dr. Kochakian, has already begun (Fig. 3).[12] I do not know how many potent compounds we have missed because of the arbitrary time limit of the test. Some have been supplied to us in such small amounts that the standard dose of 0.1 mg. per rat per day for seven days permitted assay in only five animals.

Finally, Dr. Eisenberg and I have both felt very strongly that the levator ani test is far too crude to be taken as anything but a screening procedure. We have used it to identify promising compounds. Any compound which appears anabolic and only weakly androgenic is then submitted to more definitive tests, such as nitrogen balance. If the compound still appears to be a potent anabolic agent it is next screened for androgenicity in man. This subject, too, has become a little more complex recently due to the demonstration of "incomplete androgens." In general one can detect androgenic activity very easily by observing the effect of the test agent in males who lack androgen, e. g., patients with hypopituitarism or hypogonadism or normal young boys. Under these circumstances potent androgens quickly induce phallic stimulation and growth. We now have at least one highly potent androgen that produces full growth of the penis or clitoris but seems to have remarkably little effect upon voice or hair growth. This compound is fluoxymesterone (Halotestin, Upjohn), which is 9α-fluoro-11β-hydroxy-17α-methyltestosterone. In this compound, as in the corticoids, the introduction of a fluorine atom in the nine position has greatly intensified androgenic activity. We have found this compound in doses of 2 to 4 mg. per day taken as swallowed tablets effective for maintaining phallic growth and activity in eunuchoid males.[13] It is now being studied in the treatment of far-advanced carcinoma of the breast, and surprisingly, although it is no less effective than testosterone propionate as an anticancer agent, it has produced an incomplete type of androgenicity. Although the clitoris has become greatly enlarged there has been little effect upon libido and surprisingly little hair growth. It is thus apparent that not all androgenic end-points necessarily parallel each other.

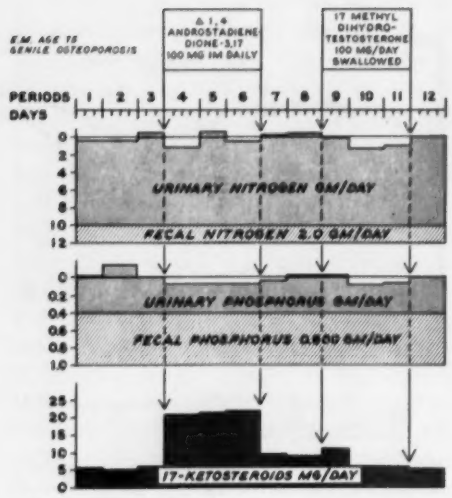

Fig. 4.—Anabolic efficacy of 1,4 androstadiene-dione and 17-methyl-dihydrotestosterone.

At the present time we have a number of compounds that have gone through the levator ani test and have proved anabolic in human balance studies. These are 17α-methylandrostenediol; Testololactone; 19-nortestosterone and 19-nortestosterone cyclopentylpropionate; 17α-ethyl-19-nortestosterone; 17α-methyl-19-nortestosterone; 17α-methyl-Δ^1-testosterone; $\Delta^{1,4}$-androstadienedione-3,17 (Fig. 4); $\Delta^{4,6}$-androstadienedione-3,17 (Table), and preliminary information suggests that 17α-methyl-$\Delta^{4,6}$-androstadiene-17β-ol-3-one may be similarly potent.[14] All of these have been studied in the rat, and the most promising have also been studied in man, namely methylandrostenediol; $\Delta^{1,4}$-androstadienedione-3,17; 19-nortestosterone (Fig. 5), and 17α-ethyl-19-nortestosterone (Fig. 6). All of these are potent anabolic agents in man, and in the case of methylandrostenediol we have long-term experience which indicates that the agent may be given for as long as six and one-half years with only minimal androgenicity. The compound 17α-ethyl-19-nortestosterone has been studied for about two years; with it we have been able to separate anabolic and androgenic activity fairly quantitatively. In prepuberal boys 1 mg. per kilogram of body weight often induces genital development, while 0.5 mg. per kilogram causes no growth of the phallus. The latter dose, however, is effective for increase in stature.

In summary, the growth of the levator ani muscle, if tested long enough after castration of the immature male rat, correlates well with anabolic activity in man. It is, however, only a screening technique, designed to identify promising agents, the anabolic activity of which must be established by more definitive methods, such as nitrogen balance. While anabolic and androgenic activity can easily be dissociated in short-term laboratory conditions in the rat, complete dissociation of these actions has not yet been achieved in man.

University of California Hospital (22).

Steroids Which Induce Significant Growth of the Levator Ani Muscle

No. Rats	Compound (Dose/Day, Mg.)	Levator Ani Wt., Mg.	Sem. Vesicles Wt., Mg.	Outcome in Man
9	Androstenediol-3β, 17β (0.1)	46 ± 3.1	24 ± 1.6	Not tested; androgenic in rat
9	17α-Methylandrostenediol-3β, 17β (0.1)	47 ± 4.3	12 ± 1.2	Widely tested; anabolic; mildly androgenic
5	Testololactone (5)	31 ± 2.7	8 ± 0.8	Not tested; action over in 5 days in rat
8	$\Delta^{1,4}$-Androstadienedione-3, 17 (0.1)	44 ± 1.3	10 ± 0.9	See Fig. 4; only weakly anabolic; not studied further
8	$\Delta^{4,6}$-Androstadienedione-3, 17 (0.1)	42 ± 3.0	11 ± 0.9	Not available for further study
x	19-Nortestosterone (0.05)	37.2 ± 2.53	7.3 ± 0.67	Anabolic; strongly androgenic
5	19-Nortestosterone cyclopentylpropionate (0.1)	90	25	Anabolic; strongly androgenic
x	Methylnortestosterone (10)	57.4 ± 3.44	30.0 ± 2.29	Not studied; androgenic in rat
x	Δ^1-Methyltestosterone (1.25)	* 29.4 ± 1.75	8.9 ± 0.56	Not studied; higher doses androgenic in rat
x	17α-Methyldihydrotestosterone (1.)	* 20.6 ± 1.34	6.0 ± 0.46	See Fig. 4; mildly androgenic in man

* Hershberger test.

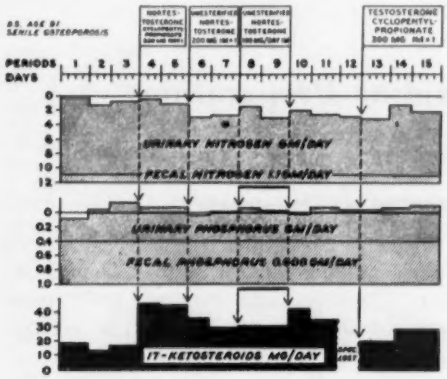

Fig. 5.—Anabolic efficacy of 19-nortestosterone and its cyclopentylpropionate.

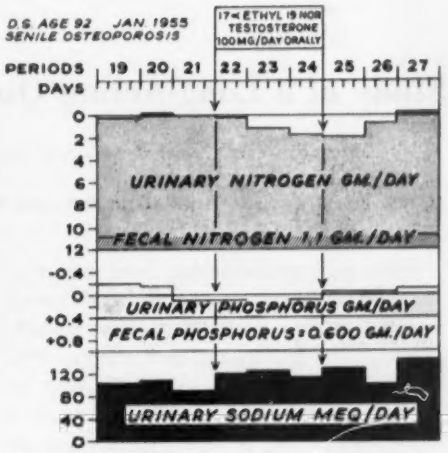

Fig. 6.—Anabolic efficacy of norethandrolone.

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Study of a Long-Acting Quinidine Preparation:

Experience in Normal Subjects and in Patients with Myocardial Abnormality

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Since 1918 quinidine has been used successfully in the treatment and prevention of various cardiac arrhythmias, particularly extrasystoles, paroxysmal tachycardia, atrial fibrillation, and flutter. Since the oral ingestion of quinidine derivatives reach a blood plasma peak relatively quickly and the concentration following a single dose falls rather rapidly,[1-5] it is necessary to administer not only multiple daily doses but frequently night doses to maintain an effective plasma level. In order to avoid multiple doses, attempts have been made at various times to administer a slower- and longer-acting preparation. Sampson et al. (1952),[6] in an effort to find a more slowly absorbed and longer-acting preparation of quinidine, used a delayed-absorptive-coated tablet of quinidine sulfate. They gave 0.8 gm. as a single dose to five patients. The maximum quinidine level, which ranged from 2.3 to 3.3 mg. per liter (average, 2.72 mg. per liter) was reached in 5 to 12 hours. More recently Ditlefsen (1954) [11] administered a coated tablet of delayed-absorptive quinidine to 10 subjects in a dose of 0.8 gm. Peak levels ranging from 1.54 to 4.25 mg. per liter (average, 3.03 mg. per liter) were reached in 4 to 10 hours. The average plasma level after 14 hours was 1.54 mg. per liter.

In view of the recent advances in the preparation of delayed-absorptive medication, we decided to reinvestigate the possibility of producing an effective quinidine preparation which would maintain a sustained blood level. Such a preparation, if it maintained an effective plasma level, would have the distinct advantage of a relatively simple dose schedule (two or three doses per day) and avoid the night dose. Moreover, it would avoid the valleys in plasma concentration during which the arrhythmia tended to recur.

In our initial studies quinidine sulfate was the alkaloid employed. This preparation gave somewhat disappointing results with the dosage schedule used. Although a prolonged effect was produced, the plasma level did not attain the value required for a sustained therapeutic effect. We shifted, therefore, to quinidine gluconate because of its greater solubility (1:9) in water, as compared to quinidine sulfate (1:90).[7,8] This preparation would have the advantage, since it has a more dependable absorbability and a more uniform effect, of making it possible to attain higher plasma levels for a given dose of the quinidine alkaloid. The object of this study was to determine the plasma levels of a long-acting preparation of quinidine gluconate in normal subjects and in patients with myocardial disease and its efficacy in the treatment of cardiac arrhythmias.

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From the Division of Cardiology of the Philadelphia General Hospital and the Graduate Hospital and Robinette Foundation of the University of Pennsylvania. Director, Division of Cardiology, Philadelphia General Hospital, and Director, Division of Cardiovascular Disease, Graduate Hospital, University of Pennsylvania (Dr. Bellet); Associate Physician, Graduate Hospital, University of Pennsylvania, and Assistant Cardiologist, Philadelphia General Hospital (Dr. Finkelstein); National Heart Institute Trainee (Dr. Gilmore).

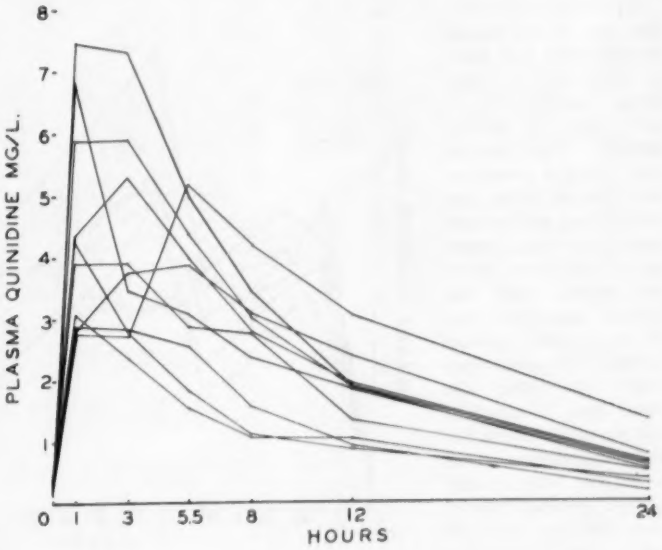

Fig. 1.—Plasma levels after oral administration of 1.0 gm. of quinidine gluconate (0.62 gm. alkaloid) in 10 normal subjects. After the administration of 1.0 gm. of regular quinidine gluconate (0.62 gm. quinidine alkaloid) the average plasma peak concentration was 4.6 mg. per liter and was reached in one to three hours. Thereafter the plasma concentration falls relatively rapidly. At the end of five and one-half hours the plasma concentration was 3.5 mg. per liter. At the end of 8 and 12 hours the quinidine content was 2.5 mg. and 1.6 mg. per liter, respectively. Negligible quantities were present in the plasma at the end of 24 hours.

Method of Study

The following cases were studied and the effects on the plasma levels determined following the oral administration of (*a*) 1 gm. of ordinary quinidine gluconate (0.62 gm. quinidine alkaloid) in 10 normal subjects (Fig. 1); (*b*) the same dose of long-acting quinidine gluconate in 10 normal subjects (Fig. 2); (*c*) two doses per day with a 10-hour interval, of 1.0 gm. each of long-acting quinidine gluconate in 5 normal subjects (Fig. 3); (*d*) the same dosage as (*c*) in 5 subjects with congestive heart failure and in 5 normal subjects, with comparison of plasma quinidine levels afterward (Fig. 4), and (*e*) the same as (*d*) in 12 subjects with myocardial abnormalities and various arrhythmias (Table). In groups (*a*), (*b*), (*c*),

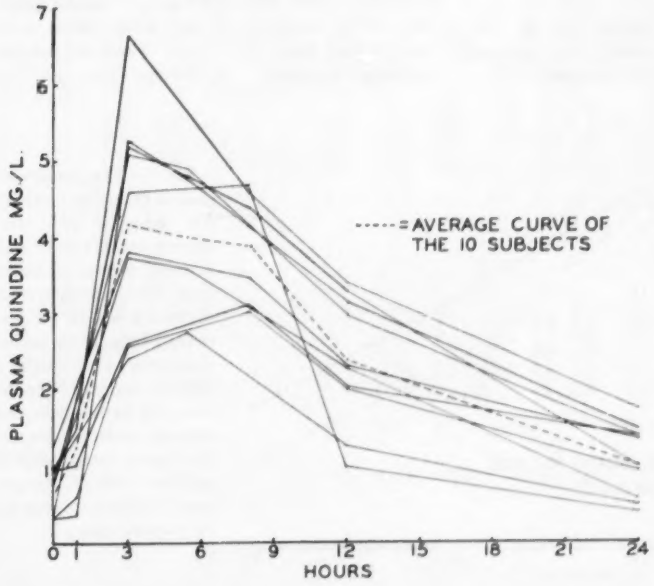

Fig. 2.—Plasma quinidine levels in 10 normal subjects after a single oral dose of 1.0 gm. of long-acting quinidine gluconate. The average peak quinidine concentration was 4.34 mg. per liter and was reached at an average of 4.8 hours. This level dropped at an average of only 1.0 mg. per liter in the following four and one-half hours. The plasma level gradually decreased, and at the end of 12 and 24 hours the quinidine content averaged 2.39 mg. and 1.07 mg. per liter, respectively.

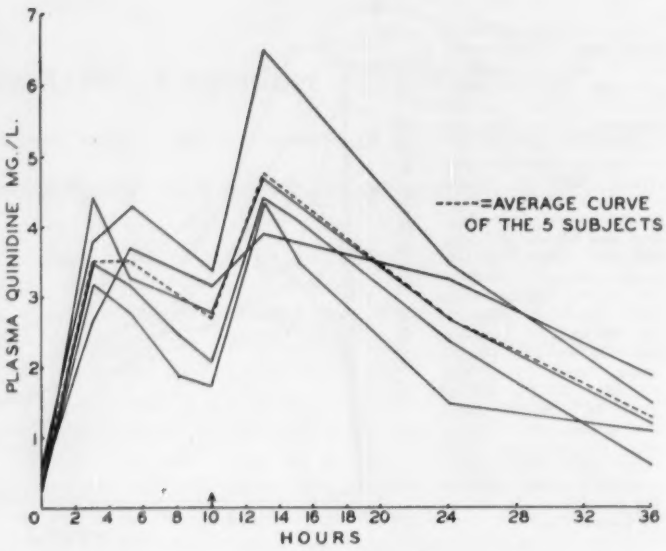

Fig. 3.—Plasma quinidine levels in five normal subjects after two doses of 1.0 gm. each of long-acting quinidine gluconate, with a 10-hour interval. The average peak quinidine concentration after the initial dose was 3.81 mg. per liter and was attained on an average of 4.0 hours. After the second dose the average peak level was 4.8 mg. per liter, and the quinidine fell more gradually than after the initial dose. Twenty-four and thirty-six hours after the administration of the first dose the average plasma quinidine content was 2.66 mg. and 1.24 mg. per liter, respectively.

and (*d*) the quinidine was given in the fasting state, before breakfast. The tablets used in this study were prepared so that each contained 330 mg. of quinidine gluconate (205 mg. of quinidine alkaloid.)*

Quinidine gluconate ($C_{20}H_{24}N_2O_2C_6H_6[OH]_5COOH.2H_2O$) contains 62.3% anhydrous quinidine, whereas in quinidine sulfate the quantity of alkaloid is 82.86%. The difference in the content of quinidine alkaloid in these two preparations should be noted in considering the doses required to produce a specific plasma level or therapeutic effect.

Normal Subjects.—These patients were free of clinically detectable heart and kidney disease. Each patient had a normal electrocardiogram, blood cell count, blood urea test, and urinalysis prior to the study. No patient received any substances giving a fluorescent reaction in the plasma other than quinidine. A test dose of 0.1 gm. of regular quinidine sulfate was given to each patient 48 or more hours before the study in order to rule out possible quinidine sensitivity. In Groups (*a*) and (*b*)

* Dura-Tab Quinidine Gluconate (S. M., sustained medication). These tablets were prepared by the Wynn Pharmacal Co., Philadelphia.

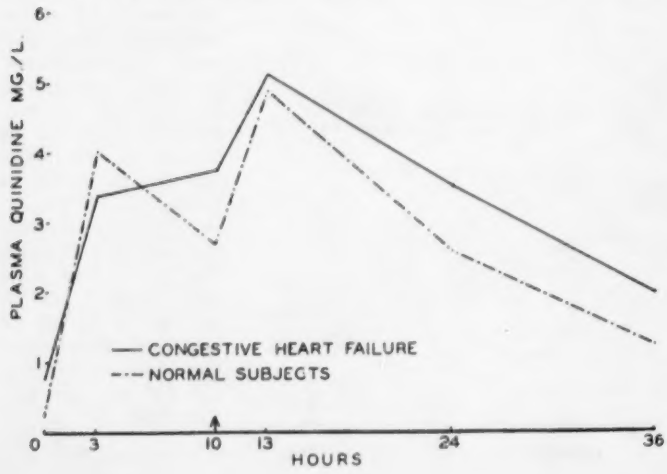

Fig. 4.—Comparison of plasma quinidine levels in five subjects with congestive heart failure and in five normal subjects after oral administration of two doses of 1.0 gm. each of long-acting quinidine gluconate, with a 10-hour interval. Note the generally higher quinidine plasma concentrations and the slower rate of fall in patients with congestive heart failure as compared to normal subjects.

Plasma Levels of Quinidine Gluconate in Patients with Myocardial Abnormalities and Arrhythmias

Case No. Age Sex	Weight, Lb.	Type of Heart Disease	Bun, Mg./ 100 Cc.	Type of Arrhythmia	Time *	Day of Treatment † 1 Dose, Gm.	1 Plasma Conc., Mg./L.	2 Dose, Gm.	2 Plasma Conc., Mg./L.	3 Dose, Gm.	3 Plasma Conc., Mg./L.	4 Dose, Gm.	4 Plasma Conc., Mg./L.	5 Dose, Gm.	5 Plasma Conc., Mg./L.	6 Dose, Gm.	6 Plasma Conc., Mg./L.	Remarks
1 54 F	198	Hypertension and arteriosclerotic heart disease; cardiac enlargement	13	Multiple extrasystoles	9 a. m. 12 noon 7 p. m.	1.0	0.18	1.0 1.0	1.76 2.66	1.0 1.0	1.96 6.84 5.10	1.0 1.0	5.20 8.48	1.0 1.0	5.82 8.48	No No	5.60	Therapeut. effective; toxicity on 5th day
2 58 F	151	Hypertension and arteriosclerotic heart disease; cardiac enlargement	13–36	Multiple extrasystoles	9 a. m. 12 noon 2.30 p. m. 7 p. m.	0.3 0.3	1.16 3.28 2.88	0.3 0.3	2.56 3.28	0.3 0.3	3.16 4.50	0.3 0.3	3.28 4.20	0.3 0.3		0.3 0.3		Therapeut. effective at high plasma levels
						Day 8		Day 9		Day 10		Day 11						
					9 a. m. 12 noon 7 p. m.	0.6 0.6	6.64 7.44	0.6 0.6	8.00	0.6 0.6	7.14 9.44	0.6 0.6	8.08					
																Day 9		
3 47 M	147	None	16	Multiple extrasystoles	9 a. m. 12 noon 7 p. m.	1.0 1.0	0.30 3.70 2.08	1.0 1.0	2.88 5.90 3.40	1.0 1.0	3.40 4.90 3.60	1.0 1.0	3.16 5.50	1.0 1.0	3.16 6.02 5.00	1.0	3.16 6.21	Promptly effective; no toxic symp. after 9 days
4 70 F	200	Hypertension and arteriosclerotic heart disease	13	Multiple extrasystoles	9 a. m. 2:30 p.m. 7 p. m.	1.0 1.0	0.50 4.30	1.0 1.0	4.40 6.12	1.0 1.0	3.90 6.92	1.0 1.0	4.40 5.20	1.0 1.0	3.48 4.48			Promptly effective; no toxic symp. after 5 days
5 76 M	140	Hypertension and arteriosclerotic heart disease; cardiac enlargement	8	Multiple extrasystoles	9 a. m. 2:30 p.m. 7 p. m.	Midnight 0.6	0.30	0.6 0.6	2.36 5.00	0.6 0.6	5.12 5.68	0.6 0.6	5.68 6.12					Promptly effective
6 55 M	120	Hypertension with cardiac enlargement	44–47	Atrial tachycardia	9 a. m. 2:30 p. m. 7 p. m.	1.0	0.58	1.0 1.0	2.66 5.28	1.0 1.0	4.90 5.40							Effective
7 67 F	150	Arteriosclerotic heart disease	15	Atrial tachycardia	9 a. m. 2 p. m. 7 p. m.	1.3	5.20	1.3 1.3	6.42 8.48	1.3 1.3	8.80 10.56							No effect at 10.56 mg./L.
8 67 F	110	Arteriosclerotic heart disease	35	Atrial fibrillation	9 a. m. 2 p. m. 7 p. m.	1.0 0.3	0.30 5.82	0.3	6.22									Converted to normal sinus rhythm after one dose
9 70 M	153	Arteriosclerotic heart disease	30	Atrial fibrillation	9 a. m. 2:30 p. m. 7 p. m.	1.0	1.08	1.0 1.0	3.10 6.64	D.C.	3.76							Not effective; developed AV nodal rhythm & vomiting at peak level of 6.6 mg./L.
10 56 F	160	Arteriosclerotic heart disease	17	Atrial fibrillation	9 a. m. 2:30 p. m. 7 p. m.	1.0 1.0	0.30 5.40	1.0 1.0	6.84 9.04	1.3 D.C.	7.54 9.32							Not effective at peak level of 9.32 mg./L.
11 71 M	100	Arteriosclerotic heart disease	74	Atrial flutter	9 a. m. 2:30 p. m. 7 p. m.	1.0 1.0	0.36 3.60	1.0 D.C.	13.68 15.52									Not effective at peak level of 15.52 mg./L
												Day 8		Day 15				
12 55 M	163	Arteriosclerotic heart disease	23	Atrial fibrillation	9 a. m. 12 noon 7 p. m.	1.0	0.30	1.0 1.0	1.26 2.36	1.0	2.08 1.26	0.6 0.6	1.68 2.98	0.6 0.6	2.48 4.20			Converted to normal sinus rhythm at 2.08 mg./L. on 2d day of therapy

* Time of day at which quinidine gluconate was given and/or plasma levels determined.
† D. C. indicates discontinued.

quinidine plasma levels were obtained prior to and at 1, 3, 5½, 8, 12, and 24 hours after the administration of the drug (Figs. 1 and 2). These patients ranged in age from 22 to 75 years, with an average age of 51.7 years. They weighed from 120 to 165 lb., the average weight being 135.6 lb. In Group (*c*), five normal subjects received a total of two doses in one 24-hour period of 1.0 gm., each, with a 10-hour interval (Fig. 3). Plasma levels were determined prior to and at 1, 3, 5, 8, 12, 24, and 36 hours after the administration of the initial dose. These subjects ranged in age from 24 to 70 years, and the average age was 47.2 years. Their weight ranged from 105 to 158 lb.; the average was 135.6 lb.

Studies in Patients with Myocardial Disease.

Group (*d*) consisted of five patients who manifested a moderate grade of congestive heart failure (Fig. 3). The ages ranged from 50 to 73, with an average of 59 years, and the weights ranged from 135 to 180 lb., with an average of 155 lb. The diagnosis was hypertensive cardiovascular disease (three cases), rheumatic heart disease (one case), and arteriosclerotic heart disease (one case). The normal subjects used for comparison consisted of patients from Groups (*a*) and (*b*). The patients in Group (*e*) manifested various types of myocardial abnormalities, including hypertension and arteriosclerotic heart disease (Table).† Six had premature contractions; two, paroxysmal atrial tachycardia; four, atrial fibrillation, and one, atrial flutter. All the fibrillators were first fully digitalized. Plasma quinidine levels were obtained before the morning dose of the drug was administered, three hours later, and usually prior to the evening dose. In view of our experience in the normal subjects it was decided to administer long-acting quinidine to this group in the form of two daily doses of 1.0 gm. (0.62 gm. quinidine alkaloid), each at intervals of 10 hours (9 a. m. and 7 p. m.). These doses were found to produce plasma levels that were within the therapeutic range (Fig. 3). Moreover, as has previously been shown, patients with myocardial damage, particularly with some degree of heart failure, manifest plasma levels that are somewhat higher and more sustained than in the normal group.[10]

Blood level determinations of plasma quinidine were performed according to the method of Brodie and Udenfriend.[9] In our laboratory the error of this method was ±0.13 mg. per liter.

Results

Effect of a Single Dose.—The effect of the administration of regular quinidine gluconate and the long-acting quinidine gluconate on the plasma quinidine levels in normal subjects is shown in Figures 1 and 2, respectively. The curves obtained in the 10 subjects of each group are superimposed. Note that after the oral administration of 1 gm. of ordinary quinidine gluconate (0.62 gm. alkaloid) the average plasma peak concentration was 4.6 mg. per liter and was reached in one to three hours. Thereafter these levels began to fall rather rapidly and after five and one-half hours averaged 3.5 mg. per liter. After the use of long-acting quinidine gluconate the average peak concentration was 4.34 mg. per liter (range, 2.76 to 6.64 mg. per liter) and was reached at the end of about five hours but was maintained for about three to five and one-half hours after the initial dose (Fig. 2). This is contrasted to the rather rapid decline in concentration following the regular quinidine gluconate after the peak concentration is reached (Fig. 1). After administration of the long-acting quinidine gluconate the plasma level dropped at an average of only 1.0 mg. per liter in the following four and one-half hours (five and one-half to nine hours after initial dose) after the peak concentration was reached. Twelve hours after the administration of the drug the quinidine plasma concentration averaged 2.39 mg. per liter. At the end of 24 hours the average plasma quinidine concentration was 1.07 mg. per liter, with a range of 0.36 to 1.76 mg. per liter.

Effects of Multiple Doses.—The effects of multiple doses on the plasma quinidine levels in normal subjects are shown in Figure 3. The average peak concentration after the initial dose was 3.81 mg. per liter (range, 3.16 to 4.4 mg. per liter) and was attained on an average of 4.0 hours after the initial dose. After the second dose the peak level was somewhat higher and the fall more gradual than after the initial dose. Twenty-four hours after the administration of the first dose the average plasma quinidine level was 2.66 mg. per liter, with a range of 1.48 to 3.48 mg. per liter, or 70%

† One subject had both atrial fibrillation and premature beats.

of the initial peak level. The average plasma quinidine concentration 36 hours after the beginning of the experiment was 1.24 mg. per liter, the range varying from 0.58 to 1.88 mg. per liter. This represents 32% of the initial peak concentration.

The effect of a two-dose schedule (1 gm. each dose of long-acting quinidine gluconate, with a 10-hour interval) in congestive heart failure is shown in Figure 4. Note that the initial level (average in five patients) attained at the end of three hours was 3.3 mg. per liter and that this level increased to 3.8 mg. per liter at the 10-hour period. After the administration of the second dose a peak level of 5.3 mg. per liter was attained three hours after the second dose and tended to decline slowly. Note that a relatively effective level (3.8 mg. per liter) was still present at the end of 24 hours. Thirty-six hours after the initial dose the serum level was 2.2 mg. per liter. Note that the plasma levels were higher and were maintained for a longer period in subjects with congestive heart failure as compared to the normal group. This is in keeping with previous data.[10]

Effects of a Two-Dose Schedule per Day in Patients with Cardiac Arrhythmias.—The effects of the plasma quinidine levels in this group are shown in the Table. Eleven of these patients received the alkaloid in exactly the same dosage and time interval as the normal group. Because of the presence of congestive failure and uremia one patient received smaller doses (0.3 gm. b. i. d. for five days and 0.6 gm. b. i. d. for three days), with resulting effective plasma levels. The 12 patients of this group manifested the following cardiac arrhythmias: premature contractions (six patients), paroxysmal atrial tachycardia (two patients), atrial fibrillation (four patients), atrial flutter (one patient). One of these patients manifested both premature beats and paroxysmal atrial tachycardia. Quinidine plasma levels were determined before and at the following intervals after the administration of the morning dose: three to five hours later and immediately before the evening dose.

The quinidine levels at which abolition of the arrhythmias occurred were within the range usually observed with quinidine sulfate. The following data are presented to show the effect of the long-acting preparation: Quinidine gluconate was successful in abolishing premature contractions in the six patients to whom it was administered (over a period of 3 to 12 days). The quinidine levels at which the extrasystoles disappeared ranged from 1.76 to 9.44 mg. per liter. In one of these patients the abolition occurred at high plasma levels.

One patient with atrial tachycardia was converted to normal sinus rhythm on the third day, at a plasma level of 5.40 mg. per liter. Conversion was unsuccessful in the second case, therapy being stopped after three days, with a quinidine plasma level of 10.54 mg. per liter.

Two cases of atrial fibrillation were converted to normal sinus rhythm at plasma levels of 2.08 and 5.82 mg. per liter on the third and first days of therapy, respectively. They were successfully maintained in normal rhythm on a dose of 0.6 and 0.3 gm. of quinidine gluconate twice a day. In the other two subjects with atrial fibrillation quinidine therapy was stopped because of nausea and vomiting, with a quinidine plasma level of 9.3 mg. per liter, in one case, and the development of similar gastrointestinal manifestations and coupled ventricular extrasystoles, with a plasma quinidine level of 3.76 mg. per liter, in the other case.

Comment

Plasma Levels with Regular Quinidine Sulfate.—After the oral administration of regular quinidine sulfate in the strength of 0.2, 0.4, and 0.6 gm. the average peak concentration was 0.8, 1.3, and 2.0 mg. per liter, respectively. The plasma peak levels are reached in one to three hours and are maintained for about two to three hours.[1-5] At the end of 12 hours significant plasma

levels are still present. After 24 hours only traces of quinidine are found in the plasma in most instances.[3]

Delevett and Poindexter[1] gave a single oral dose of 1.0 gm. of quinidine sulfate (82.28% anhydrous quinidine) to 20 patients and found the average serum quinidine level at three hours to be 2.6 mg. per liter and at eight hours, 1.4 mg. per liter. No patient had as much as 40% of the peak level at the end of 12 hours, and less than 10% of the maximum concentration could be detected in the plasma at the end of 24 hours in most cases. Other investigators using quinidine sulfate have reported similar curves.[1-5] We ourselves gave 0.8 gm. of quinidine sulfate to 10 normal subjects and found that the range and the average peak concentration were similar to those obtained by other observers. The plasma concentration varies considerably in different subjects; these were apparently not related to variations in the weight of the patient. They may be due to differences in absorption and excretion.

Sampson et al.,[6] in using a delayed absorptive-coated tablet of quinidine sulfate, found the maximum concentration in the blood plasma to be similar to those obtained with an equal dose of regular quinidine sulfate. There was a delay in the appearance of the drug in the plasma of about two hours, and the maximum concentration occurred in two to nine hours. After a single oral dose of 0.8 gm. of this preparation (0.66 gm. quinidine alkaloid) he obtained average blood levels of 2.1 mg. per liter at 5 hours, 2.4 mg. per liter at 8 hours, and 2.3 mg. per liter at 12 hours. No figures were given for 24 hours, and the level at 1½ to 2 hours was negligible. Ditlefsen[11] administered a delayed-absorptive quinidine sulfate preparation to 10 subjects in a dose of 0.8 gm. The average peak plasma quinidine concentration was 3.03 mg. per liter and was reached in an average time of 7.33 hours. The average level after 14 hours was 1.54 mg. per liter. Small but measurable amounts were present in the plasma after 24 hours. The maximum blood concentration was found to be lower than after ordinary quinidine sulfate tablets in similar dosage.

Plasma Levels with Long-Acting Quinidine Gluconate.—In our study we used a long-acting preparation of quinidine gluconate (62.3% anhydrous quinidine). After the administration of 1.0 gm. of this preparation the average peak plasma concentration was 4.34 mg. per liter and was reached in an average time of about five hours. The average was maintained at near peak levels for the next four to five hours and then gradually decreased. At the end of 12 and 24 hours 55% and 25%, respectively, of the average peak concentration could be found in the plasma. A dose of 1 gm. of quinidine gluconate contains 623 mg. of quinidine alkaloid; this is analogous to the content in 0.8 gm. of quinidine sulfate. Comparing our results to those of other investigators using similar doses of regular quinidine sulfate we obtained a higher peak concentration; sustained plasma levels persisted for longer periods, and the fall in concentration was more gradual. Significant levels could be detected at the end of 24 hours. Comparison of our results to those reported by investigators using delayed-absorptive tablets of quinidine sulfate[6,10] in similar dosage shows that the peak concentration attained by us was higher, although the period during which the blood level was sustained was similar with all preparations. The higher plasma levels obtained by the gluconate may be the result of greater solubility and better absorption than the sulfate. After a single dose of long-acting quinidine gluconate a significant fall in the plasma quinidine concentration is observed in about 10 to 12 hours after its administration. However, a significant level averaging 2.4 mg. per liter was still present at the end of this time (Fig. 2). These findings suggest that the administration of two doses per day might suffice to maintain a therapeutic quinidine level. While it would appear that the second dose might

be administered at 12-hour intervals, it was considered more feasible to administer the second dose within 10 hours. Administration over a period of days following this schedule resulted in sufficient accumulation so that an effective quinidine level is observed in the four-hour interval period. However, when the drug is administered over a long period of time a 12-hour dosage schedule might be preferable.

In the administration to patients with congestive failure and those who had recovered from the congestive phenomenon, as well as other subjects with myocardial disease, the use of the long-acting preparation would appear to be adequate to maintain therapeutic levels. It has been shown by Brown, Holzman, and Creelman [10] that patients manifesting congestive phenomenon reach a higher plasma level, which is maintained longer than in normal subjects. Moreover, some patients, especially those with arteriosclerotic heart disease, are more sensitive to quinidine effects in that they develop therapeutic and toxic manifestations at lower levels than other groups. Because of these considerations we varied the dose and found that therapeutic levels or clinical effects in most cases could be attained after the administration of 0.3 to 1.0 gm. twice a day.

Summary and Conclusions

Ten normal subjects received 1.0 gm. of oral long-acting quinidine gluconate. The average peak concentration was 4.34 mg. per liter and was reached at an average of 4.8 hours. During the following four and one-half hours this level dropped at an average of only 1 mg. per liter. Twelve and twenty-four hours after the administration of the drug the quinidine plasma levels averaged, respectively, 2.39 and 1.07 mg. per liter.

In addition five normal subjects received a total of two doses in one 24-hour period of 1.0 gm. each at a 10-hour interval. The average peak concentration after the initial dose was 3.81 mg. per liter and was attained on an average of 4.0 hours. After the second dose the peak level was somewhat higher and the fall more gradual than the initial dose. Twenty-four and thirty-six hours after the administration of the initial dose the average plasma quinidine content was 2.66 and 1.24 mg. per liter, respectively.

The subjects with myocardial damage and arrhythmias received two daily doses of long-acting quinidine gluconate of 1.0 gm. each at a 10-hour interval (9 a. m. and 7 p. m.).

The effects in abolishing extrasystoles, atrial tachycardia, and atrial fibrillation were similar to those obtained with quinidine sulfate and occurred at comparable plasma levels.

Long-acting quinidine gluconate has given effective and sustained plasma levels in the above dosage schedule. Because the above series is relatively small, it is suggested that further clinical trials be made in order to establish more definitely the clinical usefulness of the preparation.

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Addendum

Since this paper was submitted for publication we have had further experience in the control of various arrhythmias in 18 patients whose therapy had been changed from quinidine sulfate to the long-acting quinidine gluconate. Our results have been similar to those mentioned above. Episodes of ectopic rhythm were decidedly less with the long-acting quinidine gluconate.

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Hemophilia in Negro Subjects

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Hemophilia has been described in practically all racial groups.[1-3] The number of cases reported in Negro subjects is so small that the impression is given that this disorder is rare in this racial group. To date only 15 cases in Negro subjects have been reported in which the authors have presented sufficient laboratory data to support the diagnosis.[4-11] Wintrobe[12] mentions 2 cases, but they are among the 15 already reported.[6,9] One possible reason for the small number of reported cases in Negro subjects is that these cases have been unsuspected or inadequately studied. Hemophilia is not a common disease generally, and in some parts of the country the quality of medical care for Negro patients on the average has been less adequate than for other racial groups. This paper presents 14 cases of hemophilia in Negro subjects. The study is of particular interest in that some of these cases first seen in childhood have been followed for 11 years, into young adult life, with a careful study of the changes which occurred with increasing age. A detailed study of the bone and joint changes in this group of cases has already been reported in a previous publication.[13]

Methods of Study

The hematologic methods used in this study were as follows: The coagulation time was determined by a modified Lee-White procedure.[14] The method of Quick was used for plasma recalcification test.[15] The prothrombin time was determined by the method of Quick,[15] bleeding time by the Duke method,[16] and clot retraction time and prothrombin consumption test as outlined by Hamm.[17]

In 7 of the 14 cases available for study at present an attempt was made to determine whether the specific defect was an antihemophilic globulin deficiency (AHG), plasma thromboplastin antecedant deficiency (PTA), or plasma thromboplastin component deficiency (PTC). The procedures used for these determinations are outlined below:

1. A plasma recalcification determination was performed, using 0.1 cc. of oxalated plasma from patient with hemophilia and 0.2 cc. of 0.025 M $CaCl_2$ solution.

The above mixture was placed in a water bath at 37.5 C for 60 seconds and then tilted at 15-second intervals until the plasma clotted. Normal plasma coagulated in from 90-135 seconds.

2. The PTC, PTA, or AHG deficiencies were determined by modifications of the above procedure, using Mixtures A and B.

Mixture A: 0.05 cc. of oxalated hemophilic plasma, 0.05 cc. of barium-sulfate-treated plasma[18] (which contains AHG and PTA) and 0.2 cc. of 0.025 M $CaCl_2$ solution.

The above mixture was placed in a water bath at 37.5 for 60 seconds and then tilted at 15-second intervals until coagulation occurred. If the recalcification time, which was previously greater than 135 seconds, was shortened within the range of 90-135 seconds, the barium-sulfate-treated plasma had supplied either the AHG factor or the PTA factor, since the PTC factor had been removed in the preparation of barium-sulfate-treated plasma.

Mixture B: 0.05 cc. of oxalated hemophilic plasma, 0.05 cc. of normal serum (which contains PTC and PTA,) and 0.2 cc. of 0.025 M $CaCl_2$ solution.

The above mixture was placed in a water bath at 37.5 C for 60 seconds and then tilted at 15-second intervals. If the recalcification time, which was previously greater than 135 seconds, was shortened within the range of 90-135 seconds, the serum had supplied either PTC or PTA, since AHG has been removed from normal serum.

Thus, if barium-sulfate-treated plasma corrected the prolonged recalcification time and normal serum did not we concluded that the defect was AHG. If normal serum corrected the prolonged recalcification time and barium-sulfate-treated plasma did not, we concluded that the defect was PTC, since normal serum contains both PTC and PTA, while barium-sulfate-treated plasma contains PTA and AHG. If, on the other hand, both barium-sulfate-treated plasma and normal serum shortened the recalcification time, the defect was

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PTA, since this was the only factor common to both preparations.

The current criteria which define hemophilia are (1) prolonged coagulation time, (2) prolonged plasma recalcification time, (3) normal plasma prothrombin time, (4) normal platelet count, (5) poor prothrombin consumption, and (6) deficiency of AHG, PTA, PTC, or other less well-defined components.

The 14 cases presented in this paper have been studied during the 11-year period between 1945 and 1956. Four of the cases were studied in 1947, prior to the advent of the prothrombin consumption determination. Consequently, the diagnosis in this group was established by the then existing criteria, namely, Criteria 1 through 4, listed above.

Three additional cases were seen between 1948 and 1953, one a remote cousin to the four previously mentioned patients; all of these patients met the first four criteria and in addition were shown to have poor prothrombin consumption. Since one patient in this group was a remote cousin of the four patients studied in 1947, it is extremely likely that these four patients would have exhibited poor prothrombin consumption.

Five of the remaining cases have been under our care continuously during the entire 11-year period and two additional cases have been studied since 1953. In this group of seven cases all of the above criteria were met, and the specific abnormality was found to be AHG deficiency.

Presentation of Cases

There are three known hemophiliacs in the first family (McC.). These three sons are the only children of their parents. There is a history of a bleeding tendency in the maternal grandfather. In each instance there have been numerous hospitalizations for hemarthrosis, hemorrhages into muscles, and hematuria. Hospitalization was required in one patient for an episode of rectal hemorrhage and in another for an episode of peripharyngeal hemorrhage. We have recently reported the progression of the bone and joint changes in two of the members of this family.[10] All of the three boys have been shown to have an AHG deficiency. The blood coagulation data are presented in Table 1 (Group 1).

The second family included five boys and one girl. Four of the boys have shown a life-long tendency to hemorrhage. The family history is negative for bleeders. Two of these boys died prior to our study. The eldest died at 11 years of age, after a nephrectomy in an attempt to control renal hemorrhage. The second son sustained a fall at the age of 2, which apparently resulted in intermittent convulsive seizures. These seizures recurred until his death, at the age of 13. Of the remaining three sons, one is normal and the other two have been under our care for hemophilia for the past 11 years. The elder (J. H.) has had numerous bouts of hemarthrosis and recently has developed diabetes mellitus. These hemorrhagic episodes have affected chiefly his left knee and hip. In addition there have been episodes of hemorrhages into the skeletal muscles and melena. The younger of the two (Jas. H.) sustained an injury in an automobile accident at 4 years of age, necessitating a tracheotomy because of the compression of the trachea by a hematoma involving the soft tissues of the neck. He has had numerous episodes of hemarthrosis and hematuria. For details of bone and joint changes in these brothers, see a recent publication.[10] Both of these boys have been shown to have AHG deficiency. For pertinent laboratory data see Table 2 (Group 2).

In the third family (Table 2, Group 3) there were five cases which came under our direct observation. Two of these cases were brothers (T. W. and N. W.), two were first cousins (C. W. and G. N.), and one was a third cousin two generations removed (A. L.). The two brothers and two cousins were studied on one occasion in 1947,

TABLE 1.—*Coagulation Studies*

Group*	Subject	Age, Yr.	Coag. Time Whole Blood, Min.	Plasma Recalcification Time, Sec.			Prothrombin Consumption Prothrombin Time, Sec.	
					$BaSO_4$ Plasma Added	Normal Serum Added	Plasma	Serum
1	Normal	..	6-12	90-135			13.16	35
	Control	30	9	98			13.6	49
	T.McC.	23	74	885	120	3,600	12.8	12.8
	H.McC.	21	112	940	106	3,600	13.1	13.2
	D.McC.	19	118	315	120	360	13.7	13.7
2	O.H.†	11	45					
	J.H.	22	43	628	122	4,680	14.4	13.5
	Jas.H.	19	47	898	124	5,400	13.0	13.0
4	H.L.	4	45	206			15.0	15.0
	R.T.	6	30	140			15.0	15.0
	R.L.	17	66	635	107	660	14.6	14.0
	H.C.	26	57	1,101	126	5,400	13.0	13.5

* Group 1, the first family (McC.); Group 2, the second family (H); Group 4, miscellaneous cases with no blood relationship.

† Patient died prior to this study. Coagulation time obtained from records of another local hospital.

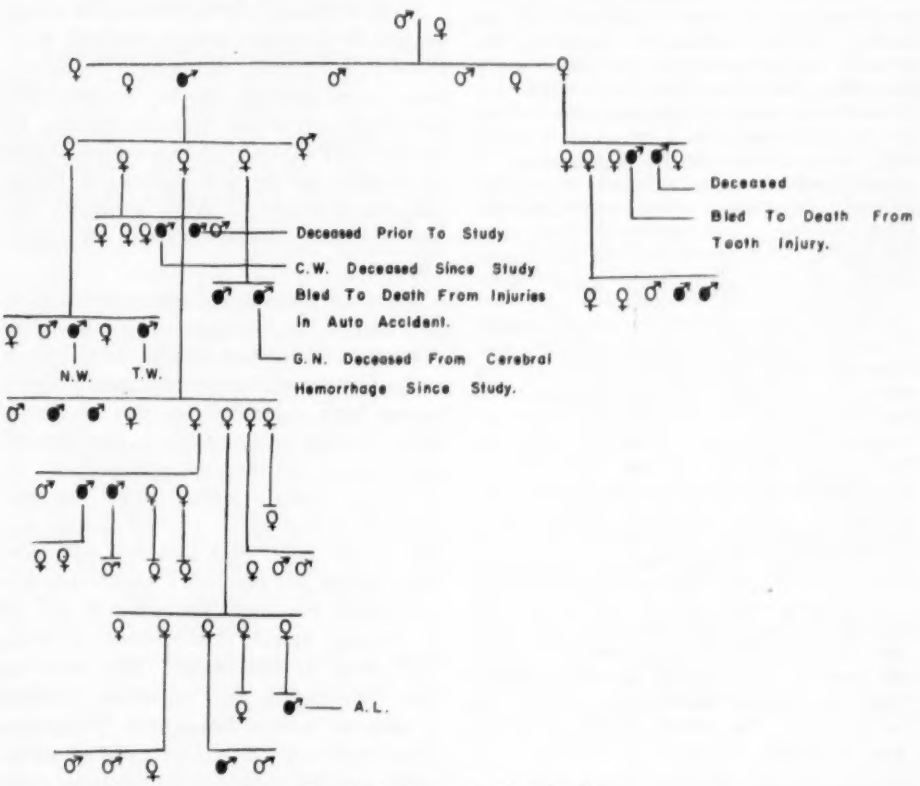
TABLE 2.—*Coagulation Studies* *

Subject	Age, Yr.	Coag. Time Whole Blood, Min.	Plasma Recalcification Time, Sec.	Prothrombin Consumption Time, Sec. Plasma	Serum
Normal	00	6–12	90-135	13–16	35
Control	30	9	98	13–6	49
T.W.(Bro.)	22	42	360	13–5	
N.W.(Bro.)	24	38	480	13–0	
C.W.(Cous.)	29	33.5	420	13–0	
G.N.(Cous.)	39	71.5	480	12–8	
A.L.(Cous.)	21 mo.	22.7	377	12–5	13.1

* Group 3, the third family consisting of two brothers, T. W. and N. W.; two first cousins, C. W. and G. N., and a remote cousin, A. L., two generations removed.

prior to the advent of the prothrombin consumption test; however, the remote cousin, 21 months old, was studied in 1953 and exhibited poor prothrombin consumption. These patients lived in a rural area and had had virtually no medical care. The eldest hemophiliac in this family had reached 39 years of age in 1947. There were numerous obvious joint deformities resulting from repeated bouts of hemarthrosis. Indeed, one of the patients had accidentally amputated his great toe[18] with an axe while chopping wood. He survived this accident without medical care. Table 2 reflects the ages and laboratory findings of the four patients at the time of study, in 1947, and the 21-month-old child studied in 1953. We have since learned that two members of this family (C. W. and G. N.) have died from hemorrhage incident to injuries sustained in an automobile accident. In this family there is a typical genealogical pattern, which is presented in the Figure.

The remaining four cases will be considered as a group (Group 4), although there is no blood relationship between these persons. In each the family history is negative for bleeders. Two of


Deceased
Bled To Death From Tooth Injury.
Deceased Prior To Study
C.W. Deceased Since Study Bled To Death From Injuries In Auto Accident.
G.N. Deceased From Cerebral Hemorrhage Since Study.
N.W.
T.W.
A.L.

Genealogical tree of third family.

these cases were seen on the pediatric service in our hospital.

The first case (H. L.) was first studied as a result of prolonged bleeding for a two-week period after circumcision at the age of 3 months. There were several hospitalizations for hemarthrosis resulting from falls. He finally died at age 6 years, from a subdural hematoma resulting from a blow on the head while at school.

The second patient in this group (R. T.) is one of two brothers. The other brother is normal. We studied this patient on his first and only hospital admission, at age 5 years, because of nontraumatic hemarthrosis.

The third patient in this group (R. H.), age 17 years, is the only child of his parents. His history indicates frequent episodes of hemarthrosis; three of these bouts of hemarthrosis and one episode of hematuria have required hospitalization since 1952. At present there is limitation of motion of the left knee and hip. This patient was demonstrated to have an AHG deficiency.

The fourth patient in this group (H. C.) is 26 years of age. He was first seen on the urologic service at the age of 24, with an obstructive uropathy. This obstructive uropathy was caused by hemorrhage into the prostate gland which was the result of a prostatic massage by a physician. The physician was not aware that the patient was a hemophiliac. The patient's past history at that time revealed only one previous bleeding episode, at the age of 11, resulting from a cut on his forehead, which was controlled by the administration of several blood transfusions. Physical examination revealed a limitation of motion around the right elbow. He was in acute retention for seven days, and despite multiple whole-blood and fresh-frozen-plasma transfusions, had shown no improvement of this condition. The urologist was of the opinion that surgery was indicated despite the patient's hemorrhagic diathesis. The patient was given antihemophilic plasma until the coagulation time was within normal limits, and then suprapubic cystostomy and perineal prostatectomy were performed. Prior to surgery it had been ascertained that the patient's deficiency was AHG. The patient's postoperative course was stormy, with several episodes of shock due to blood loss; however, the bleeding was effectively controlled as soon as we demonstrated that the effect of the antihemophilic plasma was short-lived and that it was necessary to repeat the infusions at two- to four-hour intervals. During this hospitalization he received 28 units of fresh whole blood (500 cc. each) and 15 units of antihemophilic plasma (Hyland).* There has been one hospitalization since, in 1956, for hematuria. The patient's physical condition is good at present.

* Hyland Laboratories, Los Angeles.

See Table 1 (Group 4) for laboratory findings on these four patients.

Comment

A review of the literature indicates that only 15 authentic cases of hemophilia in Negro subjects have been previously reported. The question is raised as to whether this is an accurate reflection of the frequency of this disorder in Negro subjects. In a predominantly Negro hospital population, 10 of the 14 cases reported in this paper were encountered among routine hospital admissions over a period of 11 years. The other four cases reported in this paper were studied elsewhere. With this incidence of hemophilia in our routine hospital admissions, it is our opinion that this disease must be seriously considered as a diagnostic possibility in hemorrhagic diatheses and in obscure arthritides in Negro subjects.

Seven of these fourteen patients, in whom the specific deficiency was ascertained, were found to have AHG deficiency. Therefore, these seven patients can be unequivocally considered as having true hemophilia, as opposed to PTC or PTA deficiencies. These seven cases are the first reported in Negro subjects in which the AHG deficiency has been specifically demonstrated, to our knowledge.

A typical genealogical tree was found in only two of the family groups presented in this paper. In the first family (McC.) there was a history of the maternal grandfather's having been a bleeder, but there were no other bleeders in the family to their knowledge, except the three boys mentioned. In the third family presented there were five bleeders studied by us. It is of interest that two of the boys were brothers, two were first cousins, and the fifth a third cousin two generations removed. There is a history of 17 bleeders in this family, some of whom died prior to our study. The other six cases reported in this paper are classified as sporadic cases of hemophilia. It has been established that while many cases of hemophilia have a typical family history, with

bleeders among brothers, uncles, and grandfathers, many cases have to be classified as sporadic cases.[20,21] Several theoretical explanations for sporadic cases have often been offered, as follows[22]: 1. Continued inheritance in the female through several generations, all males having by chance escaped. An example of this phenomenon may be found in the genealogical tree of A. L., presented in this paper. This male is four generations removed from a maternal great-great-grandfather, who was a bleeder; the trait was transmitted for three generations through females. 2. That these cases arise de novo. 3. That the genealogic tree is inaccurate, owing to illegitimacy.

The clinical course of these 14 patients is no way different from that described for patients with hemophilia in other racial groups.

Summary and Conclusions

Fourteen cases of hemophilia in Negro subjects which have been seen over a period of 11 years are reported. Four of the cases studied in 1947, prior to the advent of the prothrombin consumption test, met the following laboratory criteria: (1) prolonged coagulation time, (2) prolonged plasma recalcification time, (3) normal plasma prothrombin time, and (4) normal platelet count. Three additional cases were studied between 1948 and 1953; one of these three cases was a remote cousin of the original four studied in 1947. These patients met the above criteria and in addition exhibited poor prothrombin consumption.

In the remaining seven cases all of the above criteria are met and the specific defect was found to be an antihemophilic globulin (AHG) deficiency. These are the first Negro subjects in which this defect has been specifically demonstrated.

Our experience with hemophilia in Negro subjects suggests that this disorder may occur with greater frequency in Negro subjects than is reflected by the medical literature on this subject and that the clinical course of the disease is identical to that described in other racial groups.

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Treatment of Acute Gouty Arthritis with Demecolcine

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Demecolcine (desacetylmethylcolchicine) is one of a number of alkaloids which have been isolated from the plant Colchicum autumnale, which is also the source of colchicine. The chemical structure of demecolcine differs from colchicine only in that a methyl group replaces the acetyl group at the N position of the colchicine molecule (Fig. 1).[1,2]

Numerous studies of the pharmacological effects of this drug in animals have been reported.[1,3-5] It has been used in doses of 3 to 20 mg. daily for the treatment of patients with chronic myelogenous leukemia and other neoplastic diseases. Gastrointestinal disturbances, so commonly seen following the ingestion of much smaller doses of colchicine, have not been noted.[3,4,6] Skin rash, depilation, and bone marrow depression, manifested by leukopenia, thrombopenia, and anemia, have occurred in some of these patients.[3,4]

Because of the chemical similarity of demecolcine and colchicine, we decided to observe its effect in the treatment of patients with acute gouty arthritis.

Recently we reported our initial observations with demecolcine given orally to patients with acute gouty arthritis.[7] Nine of ten patients had excellent subjective and objective improvement of their arthritis without experiencing gastrointestinal disturbances. No other significant undesirable reactions were noted. Favorable response of acute gouty arthritis in 20 patients treated with demecolcine intravenously has also been reported.[8] The only undesirable reaction noted was the appearance of diarrhea in two patients of this group. There was no report of hematological studies.

Alopecia with loss of about 90% of the scalp hair has been reported in one patient about two weeks after he took 14 mg. of demecolcine in a 24-hour period for the treatment of an attack of acute gouty arthritis. Nausea, vomiting, and watery diarrhea also occurred. No hematological changes were observed.[9] Four or five patients with acute gouty arthritis treated with this drug by the oral route by Levin et al. showed satisfactory response without undesirable reactions.[10]

Our studies have been continued to include a total of 26 patients with acute gouty arthritis. Two of these patients, who received larger doses of this drug than the others because of frequent recurrent attacks

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The Ciba Pharmaceutical Products, Inc., Summit, N. J., supplied the demecolcine (Colcemid) used in this study.

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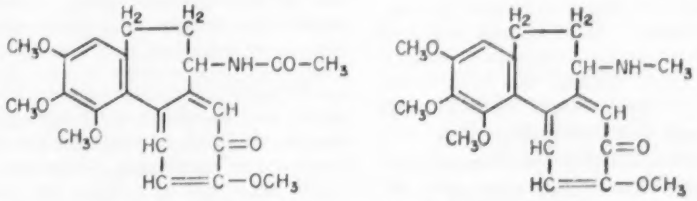

Fig. 1.—Comparative structures of colchicine and demecolcine.

Summary of Male Patients

Case	Age, Yr.	Uric Acid, Mg./100 Cc.		Demecolcine, Mg.	Response	Undesirable Reactions
		Pre-Therapy	Post-Therapy			
1 (10 patients previously reported [7])		7 of 9 elevated	No significant change	5–8	9 out of 10 patients had favorable response	1 had mild nausea, 1 had transient rash
11	33	6.7	--	8	Fair	Mild diarrhea
12	28	9.7	--	6	Complete relief	None
2d attack (2 mo. later)				10	Complete relief	None
13	54	6.4	--	6	Complete relief	None
14	48	6.0	--	2	Complete relief	None
15	44	6.8	--	10	None	None
16	35	12.2	12.0	8	Complete relief	None
17	60	7.6	8.0	10	Complete relief	None
2d attack (1 wk. later)				8	Complete relief	None
18	60	8.5	8.2	8	Complete relief	None
2d attack				8	Complete relief	None
19	39	7.4	10.4	8	Fair reduction of swelling & redness	None
20	62	10.2	11	5/17, 5 5/21, 5	None None	Mild diarrhea
21	45	9.5	--	8	Complete relief	0
22	64	10.7	10.7	8	Fair; some pain relief	0
23 1st attack (polycythemia vera)	63	10.2	10.6	See Case 23	Complete relief	See Case 23; Figs. 2,3,4.
24 (1st attack)	71	9.9	9.6	See Case 24	Complete relief	See Case 24; Fig. 5
25	74	7.8	--	8	None	0
26 (ulcerative colitis)	42	7.9	7.2	8	None	0

of acute arthritis, developed severe hematopoietic depression and depilation following this intensive therapy.

Material

Patients with proven gouty arthritis were chosen for this study. Of this group, one had gout associated with polycythemia vera. All of these patients had exquisitely tender hot swollen joints, and in some there was a past history of response to treatment with colchicine. The serum uric acid level was elevated in 22 of the 25 patients in whom it was obtained. Other findings, such as tophi and x-ray evidence of bone changes compatible with gout, were present in some patients.

Before treatment was instituted complete blood cell counts and serum uric acid values were obtained in most patients. These studies were repeated after treatment (Table).

Route of Administration and Dosage

Demecolcine was administered by the oral route. A total initial dose of 8-10 mg. was given to 20 of these patients for a single attack of acute gouty arthritis. Five patients received a total dose of 5 or 6 mg., and one patient was given only 2 mg. The dose of 8-10 mg. was chosen empirically, and because the initial responses were good this dosage plan was retained for treating most patients. Some patients were given 1 mg. of the medication every hour for a total dose of 8 mg.; some received 5 mg. initially, followed by 1 mg. every hour for three doses, and others were given 8-10 mg. in a single dose. The response to each method was equally rapid and equally good. Except for one patient, who was given only 2 mg. with excellent response, the effects of small doses of demecolcine have not been studied, and it is possible that such smaller doses may be sufficient for treatment of acute gouty arthritis and might reduce the chances of undesirable reactions. Two patients (Cases 23

Treated with Demecolcine

WBC		Subsequent Therapy with Colchicine	Response	Undesirable Reactions	Previous Therapy with Colchicine	Response	Undesirable Reactions
Pre-Therapy	Post-Therapy						
Normal	No change	1 patient	No relief	Diarrhea	8 patients	6 had fair to good relief; 2, no response	4 patients had disturbing gastrointestinal symptoms, diarrhea, nausea, vomiting
9,700	8,000	+	Fair	Diarrhea	+	+	Diarrhea
6,400	8,850	0	--	--	+	+	Nausea & diarrhea
	5,750	0			0		
5,650	6,400	0			+	+	None
7,500	8,450	0			+	Excellent	Severe nausea & diarrhea
6,600	7,250	+	None	Severe diarrhea	+	+	Severe nausea & diarrhea
8,200	7,900	0			0	--	--
7,350	9,300	+			+	Excellent	Diarrhea
7,800	6,300	+	Good	Diarrhea			
9,800	7,700	0	--	--	0	--	--
8,400	7,900	0	--	--			
8,900	7,600	+ I. V.	None	0	+	Good	Severe nausea & diarrhea
8,200	8,300	+ I. V.	None	0	+	Good to None	Severe nausea & diarrhea
11,000	9,200	0	--	--	0	--	--
8,800	8,700	I. V. and oral	Good	0	0	--	--
See Case 23, Fig. 4	See Case 23, Fig. 4	+	Excellent	Diarrhea	+	Excellent	Nausea & diarrhea
See Case 24, Fig. 5	See Case 24, Fig. 5	+	Excellent	Diarrhea	+	Excellent	Nausea & diarrhea
--	--	--	--	--	+	0	Diarrhea
7,300	7,100	0	--	--	--	--	--

and 24, Table) were given 1-3 mg. of the drug daily and received, in addition to the daily therapy, several courses of 8 mg. each of demecolcine because of frequent recurrent attacks of acute gouty arthritis. These two patients developed severe undesirable reactions, which are described below.

Response

Criteria for satisfactory response of the acute arthritis to therapy were the complete subsidence of pain, swelling, and redness of the affected joint. A patient was considered to have had no response if little or no improvement occurred either subjectively or objectively within a period of 24 to 48 hours. Acute arthritis in 5 of the 26 patients failed to respond, and in 3 others only partial improvement occurred. Three of the five patients who failed to respond favorably to demecolcine were subsequently treated with colchicine, which was also ineffective. Most patients who responded favorably to demecolcine noted improvement beginning within 4 to 6 hours after starting treatment and after 12 to 18 hours had obtained near maximum subjective and objective improvement, although the latter was delayed to as long as 24 to 36 hours in some cases.

Undesirable Reactions

Gastrointestinal Reactions.—Mild nausea was noted by two patients, and two others developed mild diarrhea.

Dermatological Reactions.—A pruritic maculopapular rash, which occurred in one patient (Case 24) after the first course of

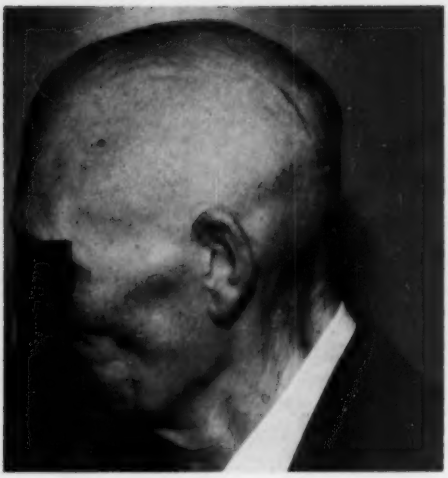

Fig. 2 (Case 23).—This picture demonstrates alopecia which appeared after demecolcine therapy.

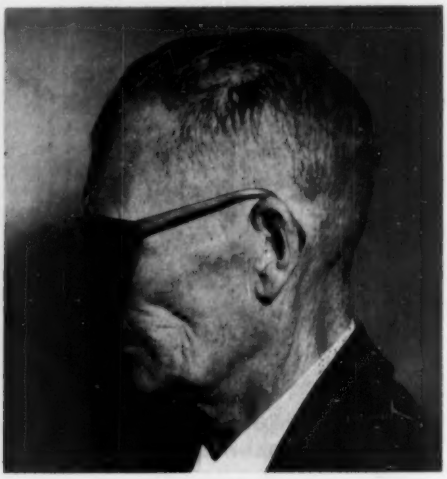

Fig. 3 (Case 23).—This picture demonstrates regrowth of hair three months after discontinuing demecolcine therapy.

therapy, subsided promptly after discontinuance of the demecolcine. This rash recurred later but only after the patient had received several more courses of therapy uneventfully.

This patient and a second patient (Case 23) developed loss of head hair (Fig. 2), absence of beard growth, and sparsity of eyebrows. Within three months after discontinuing the medication hair growth had returned to normal (Fig. 3).

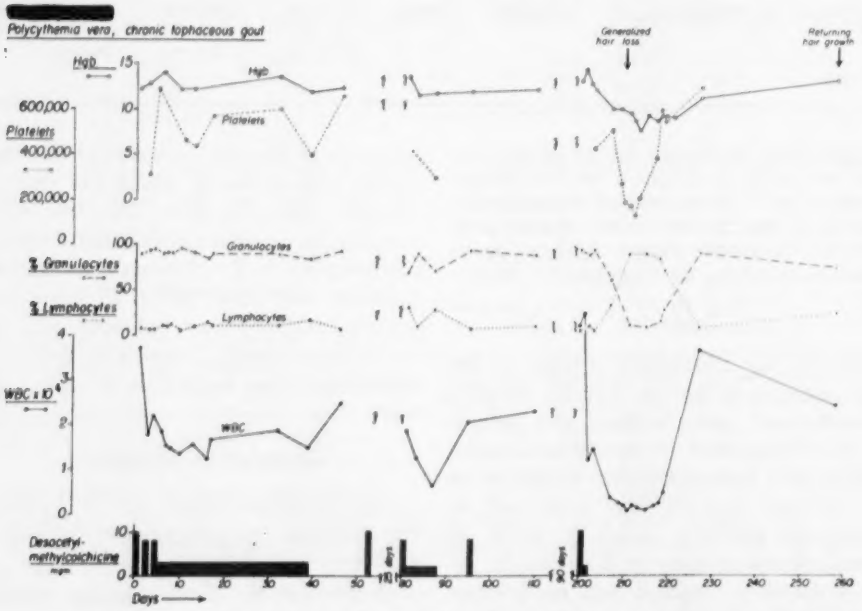

Fig. 4 (Case 23).—Data on a 63-year-old man with polycythemia vera and chronic tophaceous gout. Serial determinations of peripheral blood elements during period of demecolcine administration.

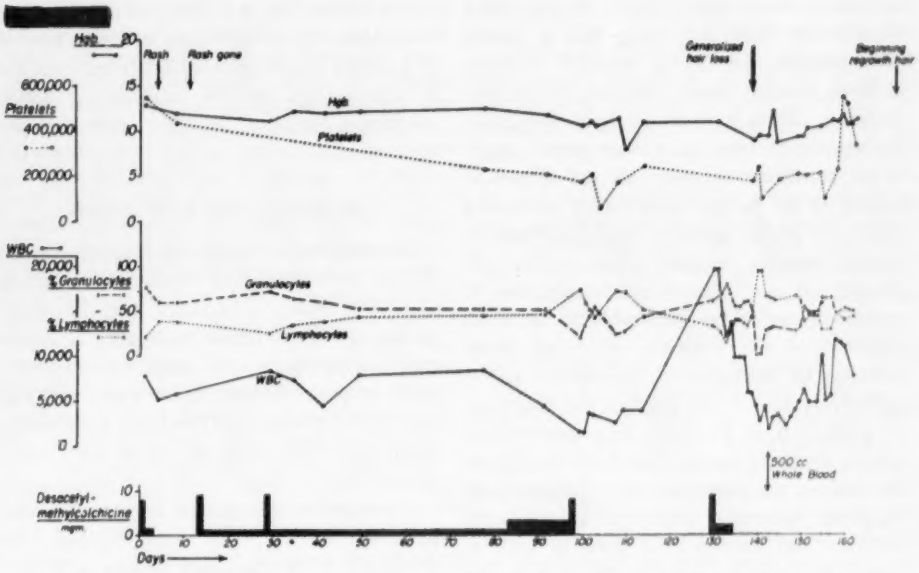

Fig. 5 (Case 24).—Data on a 71-year-old man. Serial determinations of peripheral blood elements during period of demecolcine administration.

Hematological Reactions.—The two patients (Cases 23 and 24) who had been given several courses of 8 mg. of demecolcine interspersed during the period of time when they were given daily maintenance doses of 1-3 mg. developed severe hematopoietic depression as evidenced by a fall in hemoglobin, red blood cell count, white blood cell count, granulocyte count, and platelet count (Figs. 4 and 5). When the drug was discontinued, the values for the peripheral blood elements returned to normal after a period of two to three weeks.

In both of these patients in whom hematological values had returned to normal, subsequent treatment with demecolcine in doses which previously had not caused suppression of hematopoiesis was now followed by such suppression. It is probable that the marrow which had previously been injured by this drug had not completely recovered and was, therefore, extremely sensitive to the effects of more demecolcine. This view is supported by the fact that one of the patients (Case 24) was treated again with demecolcine without side-effects 106 days after the second episode of hematopoietic suppression.

There was only minimal decrease in splenic size at the height of the hematopoietic depressive reaction in the patient with polycythemia vera.

Other Reactions.—Severe ulcerative pharyngitis appeared in the two patients reported above at the peak of the granulopenia and leukopenia. Both of these patients had temperatures ranging from 102 to 103 F. Cultures of the throat showed a mixed bacterial flora, and treatment with antibiotics seemed to be effective in controlling the pharyngitis.

Comment

Demecolcine produces rapid symptomatic and objective improvement in most patients with acute gouty arthritis and rarely causes the undesirable gastrointestinal disturbances which occur so frequently after colchicine ingestion. From this standpoint, the former drug has a very definite advantage over colchicine in the treatment of acute gouty arthritis. However, experimental studies in animals, studies in humans by others, and

our own experiences have demonstrated conclusively that this drug has a potent hematopoietic depressing reaction if given in large enough doses. Because of the undesirable effects it produces, demecolcine has limited application as a therapeutic agent in the treatment of gout. Its use should be limited to the patient with a very occasional attack of gouty arthritis with intervals of several months between these attacks. If the patient can tolerate colchicine, then it would appear to be preferable to demecolcine. Since the response of acute gouty arthritis to colchicine is considered to be sufficiently specific to warrant the diagnosis of gout,[11] it is probable that demecolcine can be similarly used. This drug should not be used in the treatment of a patient with frequent recurrent bouts of acute gouty arthritis, nor should it be used as maintenance therapy to prevent or reduce the incidence of relapses of acute gouty arthritis.

In a small group of 26 patients we have not been able to define the necessary dose of demecolcine needed to induce improvement in gouty arthritis. Much smaller doses than we have used may be sufficient to induce symptomatic and objective improvement and may thereby reduce the chances of a patient developing the undesirable effects.

One might speculate a bit further concerning the chemical structure of colchicine and its desacetyl analogue. At present the mode of action of colchicine in causing amelioration in gouty arthritis is unknown.[11,12] The fact that both colchicine and demecolcine cause similar favorable response in patients with gout demonstrates that alteration of the colchicine molecule does not necessarily prevent its effect in gouty arthritis. Numerous other colchicine derivatives have been shown to be less toxic to experimental animals than colchicine.[13-15] and clinical studies with some of these colchicine derivatives may uncover one which has potent antigout activity and none of the undesirable effects of either colchicine or demecolcine.

Elucidation of the chemical structure of the portion of the colchicine molecule needed to produce the antigout effects may even aid in clarification of the manner in which colchicine produces its effect in the patient with gout.

Summary and Conclusions

Demecolcine (desacetylmethylcolchicine) differs from colchicine chemically in having a methyl group substituted for the acetyl group in the colchicine molecule. It causes rapid symptomatic and objective improvement in patients with acute gouty arthritis and rarely produces undesirable gastrointestinal reactions, such as those seen after colchicine ingestion.

Demecolcine has potent bone-marrow-depressing activity, and pancytopenia was produced in two patients treated with frequent courses of this drug. These patients also developed generalized loss of hair on the scalp, face, and body. When therapy was discontinued in both instances there was return to normal of the peripheral blood elements. Regrowth of hair also occurred after a period of several weeks.

This drug should not be used for chronic maintenance therapy in patients with gouty arthritis, nor should it be used in those patients who have frequent recurrent bouts of acute gouty arthritis. However, it may retain a place in treating the patient who develops an occasional attack of acute gouty arthritis and who cannot tolerate colchicine. It may also be used as a diagnostic therapeutic agent for gout in patients in whom the gastrointestinal effects of colchicine are to be avoided.

Further study of other colchicine derivatives may prove fruitful in turning up a compound which retains all of the desirable effects of colchicine or demecolcine in acute gouty arthritis without retaining any of the undesirable effects of either of these drugs.

Report of Cases

CASE 23 (Figs. 2, 3, and 4).—A 63-year-old white man was admitted o the Maimonides Hos-

pital for the seventh time on July 20. There was a 12-year history of polycythemia vera and a 3-year history of acute gouty arthritis. Although treatment with colchicine usually caused improvement of the arthritis, it also caused severe nausea and diarrhea. Hematological examination on admission: Hemoglobin, 12.1 gm. per 100 cc.; white blood cell count, 37,000 per cubic centimeter; differential count, 65% polymorphonuclear neutrophils, 28% juvenile neutrophils, 6% lymphocytes, 1% monocytes. On July 23, an attack of acute gouty arthritis was treated with demecolcine, 1 mg. every hour for 10 doses. The patient's symptoms cleared almost completely by July 24, but a relapse necessitated a second course, of 8 mg. of demecolcine. His symptoms again subsided almost completely but two days later had returned once again. Treatment with 8 mg. of demecolcine was followed again by rapid improvement. Maintenance therapy of 1 mg. three times a day, beginning July 28, was instituted. On Aug. 9, the patient was completely asymptomatic and was discharged from the hospital. The maintenance dose of 3 mg. daily was continued. There had been no nausea, diarrhea, or other undesirable reactions following therapy.

On Aug. 30, he was symptom-free and the medication was discontinued.

On Sept. 13, another attack of acute arthritis was treated with a single dose, of 10 mg. of demecolcine, with excellent improvement. A recurrent attack of acute gouty arthritis, on Oct. 11, improved after an 8 mg. dose of demecolcine. A daily maintenance dose, of 2 mg., was continued for a week. The hemoglobin at this time was 13.6 gm. per 100 cc.; the white blood cell count was 18,200 per cubic centimeter, and the differential count showed 61% polymorphonuclear neutrophils, 9% juvenile neutrophils, and 30% lymphocytes. On Oct. 17, he was symptom-free. The hemoglobin was 11.8 gm. per 100 cc.; the white blood cell count was 6200 per cubic centimeter, and the differential count showed 72% granulocytes, 28% lymphocytes, and 292,000 platelets per cubic centimeter. Therapy was discontinued.

On Oct. 26, a dose of 8 mg. of demecolcine, given for another attack of acute arthritis, did not cause improvement. Phenylbutazone (Butazolidin), in a dose of 1200 mg. daily for three days, was effective. The arthritic manifestations recurred on Feb. 7, 1956. Hemoglobin was 13.2 gm. per 100 cc.; the white blood cell count was 42,000 per cubic centimeter, and the differential count showed 95% granulocytes and 5% lymphocytes. Treatment with demecolcine in a dose of 10 mg. resulted in marked relief of the gouty arthritis within four to five hours. The white blood cell count was 12,000 per cubic centimeter, and the differential count was 90% granulocytes and 10% lymphocytes on Feb. 9. Five days later, the white blood cell count was 3400 per cubic centimeter, and the differential count was 62% granulocytes and 38% lymphocytes. The platelet count was 513,000 per cubic centimeter. The patient's temperature rose to 103 F, and he complained of a painful throat. Examination revealed an ulcerative pharyngitis. A bone marrow aspiration on Feb. 17 showed a hypocellular marrow. By Feb. 18, the hemoglobin was 9.7 gm. per 100 cc.; the white blood cell count was 900 per cubic centimeter, and the differential count showed 10% granulocytes and 90% lymphocytes. The platelet count was 178,000 per cubic centimeter. The pharyngitis and fever subsided following treatment with tetracycline. On Feb. 22, the hemoglobin was 9.4 gm. per 100 cc. and the white blood cell count was 850 per cubic centimeter.

The patient's hair began falling out of his head in large amounts. Although he never became completely bald, the head hair was extremely sparse (Fig. 2). Beard growth ceased, so that he no longer had to shave, and the eyebrows and other body hair were sparse. He was discharged from the hospital on Feb. 29. The hemoglobin was 11.3 gm. per 100 cc.; the white blood cell count was 36,800 per cubic centimeter, and a differential count showed 91% granulocytes and 9% lymphocytes. Normal hair growth had returned by April 10 (Fig. 3).

CASE 24 (Fig. 5).—A 73-year-old white man had had recurrent attacks of acute gouty arthritis of 12 to 14 years' duration. Colchicine relieved his symptoms but caused severe diarrhea and nausea.

On May 11, 1955, he developed an attack of acute arthritis. Laboratory studies showed that the hemoglobin was 12.8 gm. per 100 cc.; the white blood cell count was 7700 per cubic centimeter, with a normal differential count. The platelet count was 550,000 per cubic centimeter. Serum uric acid value was 9.2 mg. per 100 cc. The patient was given 5 mg. of demecolcine orally in a single dose and 1 mg. every hour for three doses and then continued to take 0.5 mg. three times a day. Within five to six hours after starting treatment he was almost completely relieved of pain and stated that the response was much better than he previously had had with colchicine. There were no undesirable reactions. On May 14, the white blood cell count was 5100 per cubic centimeter, with a normal differential count. The patient had slight nausea, and, in addition, a pruritic maculopapular rash had appeared over his entire body. Because of this rash, the drug was discontinued. He was again seen on May 18, at which time the hemoglobin was 12.4 gm. per 100 cc., and the white blood cell count was 5900 per cubic centimeter, with a normal differential count. The pruritic rash had cleared completely by May 21. On May 23, there was a recurrence of acute gout. He was given a single

dose of 2 mg. of demecolcine and told to take 0.5 mg. daily. The arthritis improved rapidly. The pruritic rash did not recur. Another attack of acute gouty arthritis occurred on June 7, despite the daily maintenance therapy. This acute attack was treated with demecolcine in a dose of 1 mg. every hour for eight doses, and the maintenance dose was increased to 1 mg. daily. Rapid objective and subjective improvement followed. Frequent hematological examinations (Fig. 5) revealed no significant changes. The incidence of recurrences of acute arthritis appeared markedly reduced on this prophylactic regimen. About Aug. 1, 1955, there was a recurrence of acute gout, and the patient voluntarily increased the dose of the drug to 1 mg. three times a day for approximately one week. On Aug. 9, the white blood cell count was 4600 per cubic centimeter and the medication was discontinued. Because of another attack of arthritis, on Aug. 15, he was given 5 mg. of demecolcine in a single dose and 1 mg. every hour for three doses. The following morning there was marked improvement, but the white blood cell count was 1600 per cubic centimeter. The differential count showed 20% polymorphonuclear neutrophils, 2% juvenile neutrophils, 3% monocytes, and 75% lymphocytes. The platelet count was 184,000 per cubic centimeter, and the hemoglobin was 10.9 gm. per 100 cc. Questioning of the patient revealed that he had not discontinued the drug on Aug. 9, but had been taking 3 to 6 mg. daily, the exact amount not being known. Treatment was discontinued, and the white blood cell count and differential count returned to normal (Fig. 5).

The patient was admitted to the hospital on Sept. 15 for treatment of a recurrent attack of acute gouty arthritis.

Physical examination on admission showed the temperature to be 102 F. Both feet and the fingers of the left hand were hot, swollen, and red. Hematological examination showed that the hemoglobin was 13.2 gm. per 100 cc.; the white blood cell count was 21,400 per cubic centimeter, and the differential count showed 63% polymorphonuclear neutrophils, 29% lymphocytes, 1% eosinophils, and 7% monocytes. On Sept. 16, the temperature was 103 F. He was treated with demecolcine, 5 mg. at once, on Sept. 16, followed by 1 mg. every six hours. The arthritic symptoms subsided rapidly, and the temperature fell to 100 F on Sept. 18. The dose of the drug was reduced to 1 mg. on Sept. 19 and 20. He had received a total dose of 18 mg. in five days. At this time the patient's head hair was falling out in large amounts. This became progressively worse, so that there was almost complete absence of head hair and beard growth by Oct. 1.

On Sept. 20, the patient developed generalized pruritic maculopapular rash. There had been improvement in his gouty arthritis, and the pain and swelling had decreased considerably. Three days later the temperature was normal. The patient began to complain of a sore throat, and the pharyngeal mucosa was found to be red and ulcerated. On Sept. 25, there was recurrence of the acute gouty arthritis. The hemoglobin value was 10 gm. per 100 cc.; the white blood cell cunt was 4500 per cubic centimeter, and the differential count showed 6% polymorphonuclear neutrophils and 94% lymphocytes. On Sept. 26, the white blood cell count was 2800 per cubic centimeter, and the differential count showed 3% neutrophils and 97% lymphocytes. The platelet count was 117,000 per cubic centimeter. Treatment with acetylsalicylic acid (Aspirin) caused a rapid subsidence of the acute gout. The rash subsided slowly, and by Oct. 1 had cleared completely. The peripheral blood cell counts had returned completely to normal by Oct. 11. The patient was discharged from the hospital on Oct. 17, 1955 (see Fig. 5 for course of the peripheral blood values).

The patient was not seen again until Jan. 4, 1956, at which time he came to the clinic because of recurrence of the acute gouty arthritis. Growth of hair on the head and face appeared to have returned to normal. Demecolcine, in a dose of 1 mg. every hour for 10 doses, was followed by rapid improvement. Hematological examination showed a hemoglobin value to be 12.8 gm. per 100 cc.; the white blood cell count was 7100 per cubic centimeter, and the differential count showed 70% polymorphonuclear neutrophils, 4% juvenile neutrophils, 2% eosinophils, 2% monocytes, and 22% lymphocytes. On Jan. 11, the hemoglobin was 11.8 gm. per 100 cc.; the white blood cell count was 10,500 per cubic centimeter, and the differential count showed 59% polymorphonuclear neutrophils, 6% juvenile neutrophils, 4% eosinophils, 7% monocytes, and 24% lymphocytes.

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Clinical Implications of Excess Aldosterone Output

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Aldosterone is the most active corticosteroid secreted by the adrenal cortex in promoting sodium retention and elimination of potassium. In physiological amounts it is believed that aldosterone predominates in the control of sodium and potassium balance, while carbohydrate metabolism and various other functions are affected by hydrocortisone.

Secretion of aldosterone and secretion of hydrocortisone by the human adrenal cortex appear to be regulated by distinctly different mechanisms.

According to present concepts (Fig. 1) a neurohumoral substance secreted by the hypothalamus acts upon the anterior pituitary gland to release adrenocorticotropin, which stimulates the adrenal cortex to secrete increased amounts of hydrocortisone. Circulating hydrocortisone suppresses this action of the hypothalamus. There is evidence suggesting that inhibition occurs at the levels of the pituitary gland and adrenal gland too.

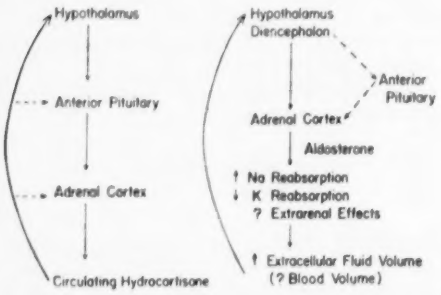

Fig. 1.—Regulatory mechanisms for control of hydrocortisone and aldosterone secretion. Present concepts of regulation derived from available evidence. Broken arrows are used when supporting evidence is only suggestive.

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Miss Anne Dowdy, Miss Julia Harvey, Mr. Way Lew, and Mr. Lee J. Poo assisted in this study.

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In contrast, aldosterone secretion appears responsive to changes in hydration and electrolyte composition of body fluids. Studies in normal men during alterations in electrolyte intake reveal a distinct inverse correlation between sodium intake and aldosterone output.[1] Potassium depletion is regularly followed by a decrease in aldosterone output,[2] while potassium loading is associated with increased aldosterone levels.[3]

The secretion of aldosterone appears to be more closely related to the volume of body fluids, especially extracellular fluids, than to serum sodium concentration. Studies by Bartter et al.,[4] Beck,[5] and Muller[6] have shown that the administration of vasopressin (Pitressin) tannate with a high fluid intake was followed by water retention, weight gain, increased urinary sodium, and decreased aldosterone levels at a time when serum sodium concentration had fallen. Increased aldosterone output after experimental bleeding in dogs[7] and man[8] suggests the blood volume as the component of the extracellular fluid most concerned with regulating aldosterone secretion. The site of the responsive volume receptor is not known, but the diencephalon has recently been suggested by Rauschkolb and Farrell[9] as the probable source of a humoral agent for the regulation of aldosterone. When saline extracts of beef diencephalon were infused intravenously into dogs, aldosterone content of adrenal venous blood rose markedly.[10] Such a neuro-

humoral agent must be able to act directly upon the adrenal cortex, since hypophysectomy does not abolish the capacity to increase aldosterone and decrease urine sodium during sodium deprivation. The smaller but consistent increases in aldosterone output for two to four days after corticotropin administration suggest that the pituitary gland may on occasion stimulate aldosterone secretion.[11]

Large doses of aldosterone administered for several days result in weight gain, fluid retention, and, ultimately, frank edema.[12] Greatly increased amounts of aldosterone have been found in urine of patients with congestive heart failure,[13] nephrotic syndrome,[14] cirrhosis with ascites,[15] and idiopathic hypoproteinemia [16] during accumulation of edema. Less striking increases are seen during static edema. Improvement in the underlying disease and diuresis are associated with a decrease in aldosterone output toward normal. These changes in aldosterone output are reflected by corresponding shifts in sodium and potassium balance. During edema accumulation urinary sodium decreases to extremely low levels and impaired excretion of sodium loads can be demonstrated. Sodium diuresis occurs with alleviation of the underlying disease. Balance studies in congestive heart failure [17] reveal a negative potassium balance during fluid accumulation, while potassium is retained during diuresis and improvement, at a time when aldosterone output is decreasing.

The correlation between aldosterone output and changes in sodium and potassium excretion is impressive. It is difficult to doubt that aldosterone has a causal role in the genesis of the electrolyte abnormalities present in most diseases associated with edema. However, other factors which have been demonstrated to affect sodium excretion may participate in edema formation.[18]

In these edematous states overhydration and sodium loading do not effectively depress aldosterone output within the normal range. This failure of normal homeostasis is strikingly demonstrated in a group of women between 30 and 60 years of age with edema of unknown origin. These patients show evidence of tension and emotional lability. Accumulation of fluid may be correlated with fatigue and emotional factors. In a few instances, premenstrual exacerbation was noted, but most patients denied any regular relation between edema and the menstrual cycle. A history of obesity or severe weight reduction about the time of onset of edema was noted on occasion. During the period of fluid accumulation five patients noted symptoms suggesting lower urinary tract infection, but no objective urologic abnormality was found in the two subjects investigated. Episodic vertigo predominated in one subject; papilledema and headaches, in a second subject, and dyspnea and wheezing in a third.

On examination no evidence of cardiac, renal, or hepatic disease could be found. Venous insufficiency in the extremities could not be demonstrated. Blood protein was within normal limits. Renal function was unimpaired. Objective tests of thyroid function were normal in all subjects studied, although several had been given thyroid medication previously. Serum sodium and potassium concentration was not remarkable. The output of 17-ketosteroids and 17-hydroxycorticoids was compatible with the age and sex of the patients.

Rigid sodium restriction was regularly followed by improvement. In several cases mild dietary indiscretions resulted in immediate weight gain and fluid accumulation. Diuretics were only partially beneficial.

Analysis of aldosterone output revealed consistent elevations in most subjects and greatly increased levels in one instance.

As noted previously, when normal subjects are given diets varying in sodium and potassium a direct correlation can be noted between the output of aldosterone and the potassium-to-sodium ratio in the urine. Since both animals and man respond to exogenous aldosterone with an increase in the potassium to sodium ratio, it is not surprising that this relationship may reflect the normal subjects' response to endogenous aldosterone. The subjects manifesting idiopathic edema ex-

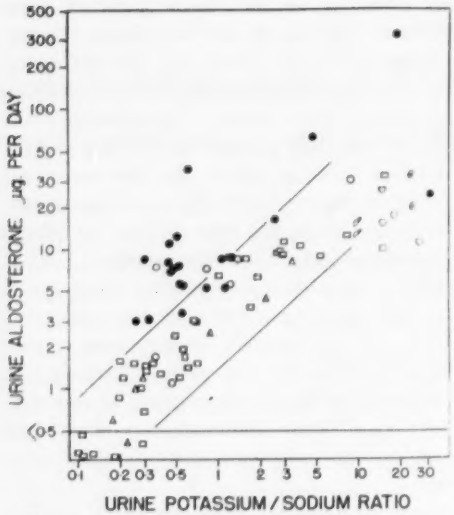

Fig. 2.—Potassium-to-sodium ratio in urine correlated with aldosterone content of same 24-hour urine collection. Normal subjects with various intakes of sodium and potassium are indicated by open circles, squares, and triangles enclosed by the parallel lines. Idiopathic edema is indicated by solid dots. Congestive heart failure, cirrhosis, and nephrotic syndrome are indicated by appropriate symbols.

crete more than sufficient aldosterone to account for the observed electrolyte output (Fig. 2). Renal response to aldosterone appears to be less sensitive than normal.

Sodium loading in patients was followed by normal elimination of sodium in four subjects, moderately impaired excretion in two subjects, and severe impairment of excretion of administered sodium in three subjects.

When one subject received 38 gm. of sodium chloride in a three-day period, no evident increase in urinary sodium or decrease in aldosterone excretion resulted.

In normal subjects, administration of sodium loads is followed by weight gain and depression of aldosterone output. This normal homeostatic mechanism fails in these patients. Although two of three patients gained a quantity of sodium sufficient to completely suppress aldosterone in normal man, aldosterone output in these patients was at control levels or higher on the third day (Fig. 3).

In these patients, episodes of edema follow emotional tension. Venning [19] and Lamson et al.[20] have noted increased aldosterone output under conditions of anxiety and stress. There is no reason to suspect that the anxiety results from the elevated aldosterone levels.

In the absence of demonstrable adrenal enlargement on tomograms, none of these subjects has been subjected to surgical exploration.

The use of total adrenalectomy to achieve diuresis of edema fluid in any disease does not appear indicated in most circumstances. Improvement in the underlying disease does not occur, and management is complicated by the superimposed adrenal insufficiency. In contrast, in Cushing's syndrome and in the potassium-losing syndrome described by Conn partial or total adrenalectomy may result in permanent cure.

In diseases associated with edema, therapy is often directed primarily toward reduction of edema.

The use of sodium restriction and diuretic agents counteracts the sodium-retaining effects of aldosterone. On occasion, a moderate reduction in edema or ascites initiates a more sustained diuresis. Thus, paracentesis in nephrosis, congestive heart failure, or cirrhosis may reduce intra-abdominal pressure and result in increased sodium excretion and loss of edema. Diminution of aldosterone

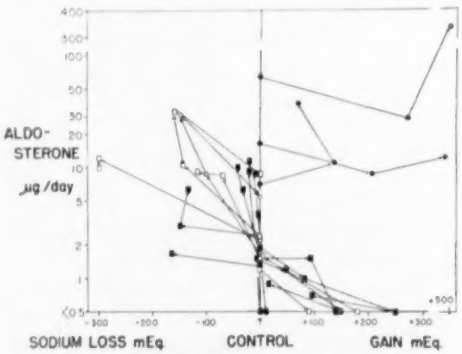

Fig. 3.—Output of aldosterone during alterations in sodium balance. Normal subjects with various intakes of sodium and potassium are indicated by open circles and all squares. Idiopathic edema is indicated by solid round dots.

output has been reported to follow paracentesis in cirrhosis.[21] In a case of congestive heart failure treated with repeated mercurial injections, Duncan, Liddle, and Bartter [22] noted that loss of edema was followed by reduction in aldosterone output.

More commonly, however, severe sodium restriction and repeated use of diuretic agents result in further increases in aldosterone levels. Sodium may virtually disappear from the urine, while potassium excretion is augmented. Repeated use of diuretics in such circumstances may succeed in only further increasing potassium elimination, while sodium excretion is unaffected. A preexisting potassium depletion, developed during the accumulation of edema, is further aggravated and may result in hypokalemia and contribute to the development of a hypochloremic alkalosis. The necessity for supplementing potassium intake is obvious, but it must be undertaken cautiously. Laragh [23] has shown that in the presence of hyponatremia ingestion of small amounts of potassium salts may cause an excessive rise in serum potassium concentration to dangerous levels.

The acute development of muscle weakness and cramps, oliguria, and azotemia following overzealous use of sodium-depleting measures has been well described. In most edematous persons hyponatremia is more commonly a result of chronic dilution. In severely ill patients with cirrhosis, nephrotic syndrome, or congestive heart failure the ability to excrete a water load is impaired. Primary water retention results in dilution of extracellular fluid and the development of asymptomatic hyponatremia. Edema may increase and is often refractory to therapy. Use of hypertonic sodium chloride intravenously may result in temporary elevation in serum sodium concentration, but dilution promptly recurs. Since the use of hypertonic saline is seldom beneficial, more satisfactory therapeutic agents are needed.

More recent measures have been directed toward correction of the primary impairment in water excretion. Use of either oral or intravenous alcohol (ethanol) to promote water diuresis by inhibiting any posterior pituitary antidiuretic factor has been successful in an occasional case.[24,25] More promising are the reports by a few observers on the use of prednisone. In a number of cases prednisone has resulted in either initiation of diuresis or in a renewed response to diuretic agents previously ineffective.[26,27] The mechanism of action of prednisone in these cases is not entirely clear. Impaired water excretion in adrenal insufficiency can be corrected by corticosteroids. Diminution in aldosterone output after cortisone therapy has been noted in nephrotic patients for a number of years, although in normal subjects corticosteroids do not appear to depress aldosterone output.[28]

Therapy directed toward improvement in the underlying disease is more rewarding than treatment of the edema itself. Complications such as thyrotoxicosis and infection should be corrected. The competent use of digitalis in congestive failure, bed rest and diet in cirrhosis, and corticosteroids in the nephrotic syndrome is indicated. Such measures are more apt to be followed by a decrease in aldosterone output, initiation of sustained diuresis, and alteration in sodium and potassium excretion in a direction favoring correction of the existing metabolic disturbance.

Summary

Aldosterone output in normal man is affected by electrolyte intake in a manner suggesting a homeostatic effect. Sodium restriction and potassium loading elicit increased aldosterone response, while sodium loading and potassium depletion are regularly followed by diminution in aldosterone output. The state of hydration, particularly in a component of the extracellular fluid volume, is an important factor in aldosterone regulation.

In edematous states (congestive failure, cirrhosis with ascites, nephrosis, idiopathic edema) aldosterone output varies with the severity of the underlying disease. Therapy aimed solely at reduction of edema may

further increase aldosterone output and lead to development of several complications. Treatment directed toward amelioration of the underlying disease appears indicated.

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The Solitary Circumscribed Pulmonary Nodule

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The solitary circumscribed pulmonary nodule seems to have become the hunting ground of the thoracic surgeon in recent years. Report after report has affirmed that primary resectable pulmonary malignancy may present itself in this form (Fig. 1).[1-24]

There is thus a good argument for removing all solitary pulmonary nodules. The argument runs as follows. Primary lung cancer has been seen in patients as young as 21 years of age. Furthermore, patients with nonmalignant nodules, including tuberculosis and other infections, are very seldom made worse by surgery. It is important to both physician and patient to know the cause of the lesion, not only from the standpoint of further treatment but also from that of prognosis.[25-29] In short, tissue diagnosis permits a reliable prognosis and usually sound therapy.

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The situation was becoming reasonably clarified until May, 1956, when Holin and associates presented at the annual meeting of the American Trudeau Society in New York City a rather remarkable survey of 666 patients with solitary pulmonary nodules found in a chest roentgenographic survey of Cleveland in 1949.[30] These 666 persons were followed for a period of five years, between 1949 and 1954, by chest roentgenograms or by operative, postmortem, or clinical findings, with 97% success. This group of patients was selected from the over 600,000 who were surveyed upon the finding by at least three, and usually all, of five examiners of a solitary circumscribed pulmonary nodule of 1 cm. or more in diameter and without roentgenographic evidence of calcification. The mean diameter of all 666 nodules proved to be 2.2 cm. The largest was 11.5 cm. in diameter. The observations at the end of five years are shown in Table 1.

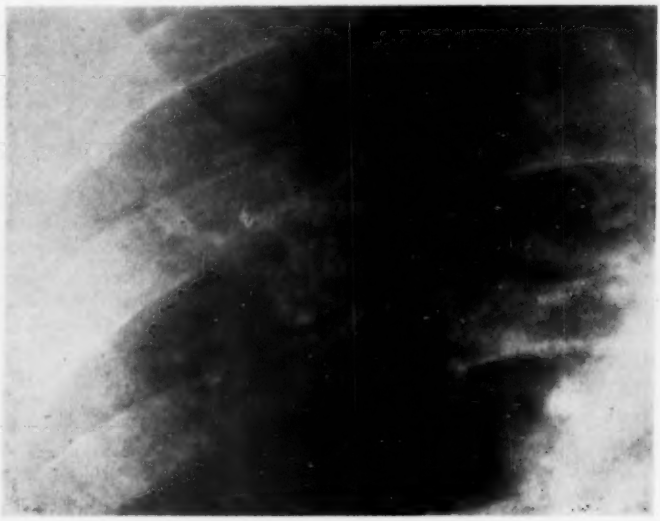


Fig. 1.—Primary bronchogenic carcinoma. A 51-year-old man was found to have a 1 cm. nodule in the superior segment of the right lower lobe on a routine premarital film taken in July, 1952, and shown here. There were no symptoms at that time. At open thoracotomy in September, 1952, a frozen section revealed squamous-cell carcinoma. A right pneumonectomy was then performed. He died at metastases seven months later.

TABLE 1.—*Solitary Circumscribed Noncalcified Pulmonary Nodules One Centimeter or More in Diameter* *

	Per Cent
Malignant	3.0
? Malignant	1.0
Tuberculosis	9.0
? Tuberculosis	9.6
Other	2.6
Undetermined	74.7
	100.0

* Holin et al.,[26] Cleveland, 1949-1954 (666 persons; 97% successful follow-up).

TABLE 2.—*Solitary Circumscribed Pulmonary Nodule—1423 Cases Proved by Operation from Literature*

	Per Cent		Per Cent
Malignant tumors	39	Granulomas	40
Primary 31		Tuberculosis 17	
Metastatic 5		Histoplasmosis 1	
Adenoma 3		Coccidioidomycosis 3	
Benign tumors	13	Lipoid 1	
Hamartoma 6		Other † 1	
Bronchial cyst 4		Questionable cause 17	
Other * 3		Other ‡	8

* Fibroma, leiomyoma, mesothelioma, lipoma, pericardial cyst, coelomic cyst, neurofibroma.
† Torulosis, brucellosis.
‡ Chronic pneumonitis, arteriovenous aneurysm, diaphragmatic hernia, loculated empyema.

The most remarkable finding was that there were only 3% with proven malignancy, plus another 1.1% with possible malignancy. Tuberculosis was said to have been the cause of the nodule in 9%, with an additional 9.6% suspected of having tuberculosis. There were 2.6% with bronchogenic cyst, hamartoma, and other rare causes of solitary pulmonary nodule. The vast majority, 74.7%, remained undiagnosed throughout the five-year period.

The age-specific death rate for cancer was essentially the same for the group with solitary pulmonary nodules as for the general population. All nodules which proved to be cancer were 2 cm. in diameter or more when first seen. Exceptions to this observation have been reported, however.[14,22,31] Surprisingly, tuberculosis was the commonest cause of death in this group. While none of the lesions were calcified at the outset, 27% had become calcified by the end of the five-year period of observation. Even excluding all males below 45, all females, and all persons with lesions showing calcification by the end of the observation period, the incidence of malignancy in this series rose only to 10%.

The incidence of histoplasmin hypersensitivity in Cleveland is about 15%, according to a recent United States Public Health Service survey. The possibility of an abnormally high incidence of histoplasmoma in this series cannot be excluded. Most of these persons were not skin-tested with histoplasmin. However, only 16 of the 666 cases were suspected of having histoplasmosis on the basis both of histo-

Fig. 2.—Bronchial adenoma. A 34-year-old man was found to have a 2×3 cm. nodule in the superior segment of the right lower lobe on a routine film taken in December, 1952. A lateral film taken at the same time is reproduced here. PPD No. 1 and histoplasmin skin tests were negative; PPD No. 2 and coccidioidin tests were positive. After preliminary biopsy a right pneumonectomy was performed in April, 1953. The patient was well without evidence of recurrence three years later.

Fig. 3.—Hamartoma.—A 41-year-old woman without symptoms was found to have a 1.4 cm. nodule in the right lower lobe on the routine film taken in March, 1956. The film shown here is a tomogram taken in March, 1956. PPD No. 1 and histoplasmin and coccidioidin skin tests were negative; PPD No. 2 test was positive. In retrospect the lesion had been present on a film taken in February, 1953, but had become considerably larger. It was removed by segmental resection in April, 1956.

plasmin hypersensitivity and the appearance of the lesion.

In striking contrast to these data, Table 2 reveals the cumulative statistics from 24 papers reporting 1423 surgically treated cases of solitary circumscribed pulmonary nodule.[1-24] In this heterogeneous group 39% were found to have had malignant tumors, either primary or metastatic; a small number, totaling 3% of the entire series, had bronchial adenoma (Fig. 2), which is included under the malignant designation because of its not infrequent malignant behavior. Forty per cent had granulomas, only half of which were proven to have had tuberculosis, histoplasmosis, or coccidioidomycosis; the cause of the rest of the granulomas was mostly undetermined. Thirteen per cent had benign tumors, the majority of which were hamartomas (Fig. 3) and bronchogenic cysts (Fig. 4); other benign tumors included fibroma (Fig. 5), leiomyoma, mesothelioma (Fig. 6), and neurofibroma. Finally, there were 8% due

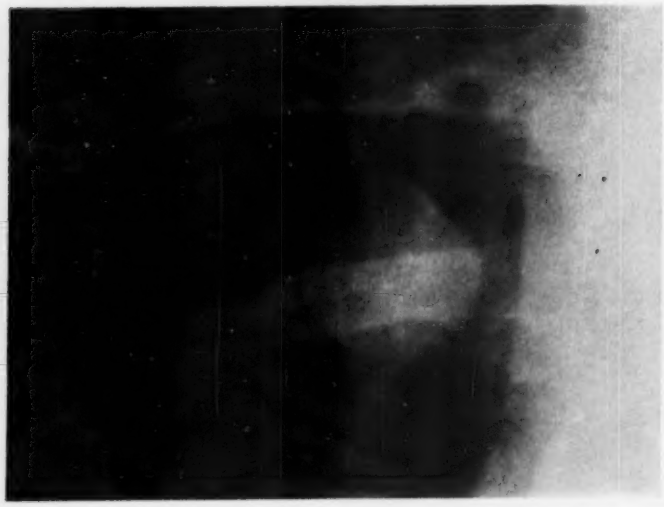


Fig. 4.—Bronchogenic cyst. A 33-year-old woman complained of dry cough for 10 years. The chest roentgenogram taken in July, 1956, and seen here revealed a 2.5 cm. nodule in the superior segment of the right lower lobe. Local resection was performed in July, 1956.

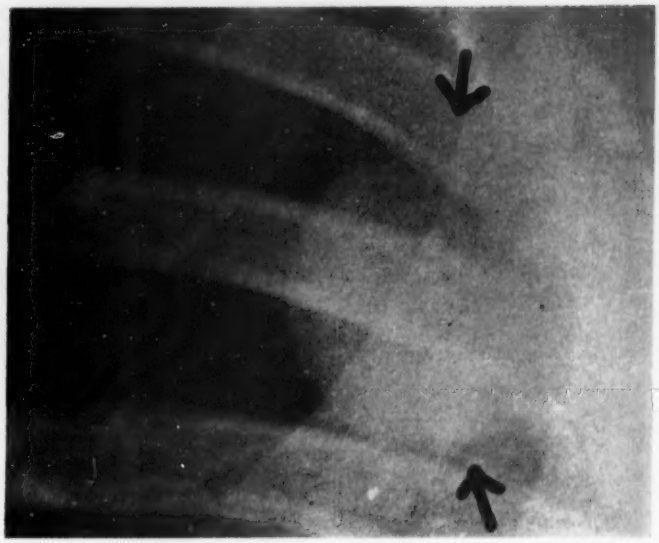


Fig. 5.—Fibroma. A 27-year-old man complained of left midchest pain intermittently for three years. The chest roentgenogram shown here was taken in May, 1952, and showed a 3 cm. mass in the superior segment of the left lower lobe. PPD No. 1 and 2, histoplasmin, and coccidioidin skin tests were all negative. Segmental resection was performed in May, 1952.

to other causes, such as chronic pneumonitis, arteriovenous aneurysm (Fig. 7), diaphragmatic hernia, loculated empyema, lung abscess (Fig. 8), and other rare disorders.

It should be emphasized that compilation of 1423 cases included some series admitting cases with nodules up to 14 cm. in diameter. In some the size was specified, and in others it was not. In some, lesions were included only if they were clearly in the pulmonary parenchyma and not in the mediastinum, pleura, or associated with the diaphragm. In some, lesions containing calcium were admitted; in others, they were excluded. In the vast majority of these reports, symptoms referable to the chest were common, and many persons sought medical care because of them.

In Table 3 are recorded the data from five series of cases on patients seen in military hospital practice.[25] While it is true that the oldest person in this group was 70 years of age, the average age for the entire group was about 30. These cases are divided into two groups, two series without any symptoms and three series with some symp-

Fig. 6.—Mesothelioma. A 32-year-old woman had a 2.5×3.0 cm. partially calcified mass in the right middle lobe on the chest roentgenogram taken in November, 1951, and shown here. The nodule was first noticed in January, 1950. PPD No. 1 and 2 and coccidioidin skin tests were negative; histoplasmin was positive. Right middle lobectomy was performed in December, 1951.

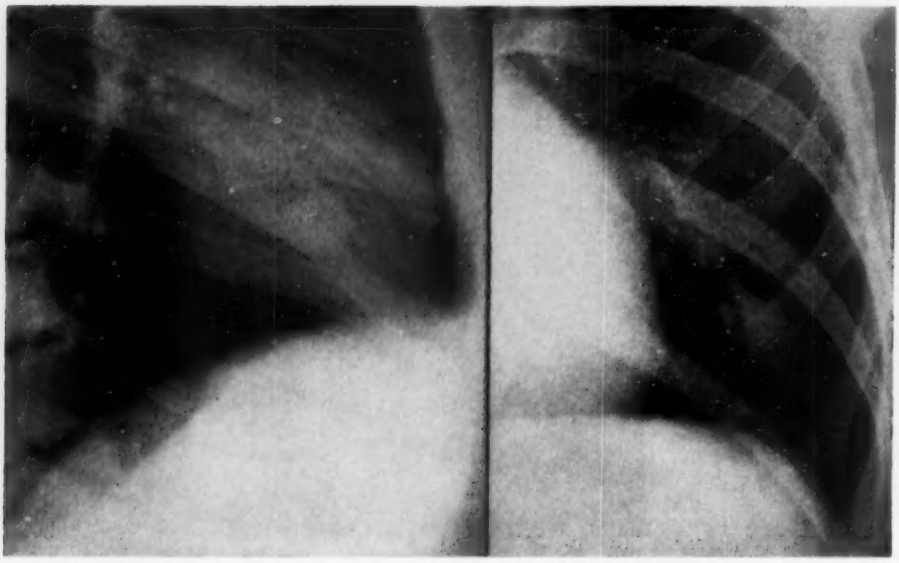
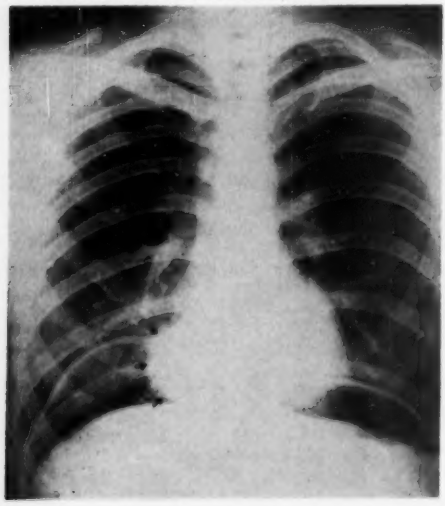


Fig. 7.—Arteriovenous aneurysm. A 22-year-old man complained of dyspnea for five years and slight hemoptysis for one week. Examination revealed slight cyanosis, a bruit over the left lower chest posteriorly, and polycythemia. The chest roentgenograms shown here were taken in February, 1956, and revealed a 2.5×3.0 cm. nodule in the anterior basal segment of the left lower lobe. Angiograms failed to reveal other pulmonary arteriovenous fistulae. In the spring of 1956 the left lower lobe was resected without incident.

Fig. 8.—Chronic lung abscess. A 21-year-old man had cough, greenish expectoration, fever, and right lower chest pain in June, 1951. After improvement, symptoms recurred and there was slight hemoptysis. The chest roentgenogram shown here revealed a 5 cm. mass in the right lower posteriomedial lung field in October, 1951. A diagnostic pneumoperitoneum is present. PPD No. 1 and 2, histoplasmin, and coccidioidin skin tests were negative. The medial basal segment of the right lower lobe was resected in November, 1951.



toms referable to the lungs. Thirty per cent of one of the latter series were reported as having symptoms referable to the chest; in the other two the proportion was not stated. In 64 persons in the two series without symptoms there were seven primary and four metastatic malignancies, or 17%. There were 145 persons in the other group, which included some patients with symptoms; of these there were 23 with primary and metastatic malignancies, or 16%. Thus, even in these two select groups of relatively young patients with no or infrequent symptoms there was still much more malignancy than was found in the Holin study. The differences in criteria for selection of cases for surgery are made particularly evident when one considers that two of these series were from the same hospital although at different periods of time.

The difference in implication between the incidence of cancer in the population survey and in all other series of cases raises a serious question. On the one hand, there is no way of being sure whether persons with

TABLE 3.—*Solitary Circumscribed Pulmonary Nodule in Military Hospitals*

Year	Author	Age Range	Av.	Symptoms	Size, Cm.	Calcium	Cases	Malignant No. Primary	Malignant No. Metastatic	Malignant Per Cent Total
1948	Effler	19-57	29	0	1+	?	24	3	1	16.7
1953	Storey	19-70	33	0	1-5	+	40	4	3	17.5
				0			64	7	4	17.2
1948	Grow	"Young"	?	±	1+	?	86	20	1	24.4
1954	Jones	"Young"	32	±	?	±	14	1	0	7.1
1955	Gregory	"Young"	?	30%	1-4	±	45	1	0	2.2
			Approx. 30	±			145	22		15.8
Total							209			

symptoms referable to the chest purposely avoided having a chest roentgenogram in Cleveland in 1949. On the other hand, the majority of the 1423 patients cited from the literature apparently came to a surgeon either because of symptoms or because a physician had seen their roentgenograms and had then referred them to the surgeon. There can be no doubt that a patient with a nodule who has been screened by a competent observer and who is then referred to a thoracic surgeon has a significantly increased risk of cancer in comparison to the person not so screened. This may be the most important clue in evaluating the wide variation in these statistics.

There is one recent much smaller survey comparable to the analysis made in Cleveland by Holin and her associates. Comstock et al. followed 88 such persons in Muscogee County, Georgia, for a median period of 53 months.[32] Only four (5%) were proved to have malignancy, all primary bronchogenic carcinoma. The observed death rate in these 88 persons was two to three times the expected, due to three deaths from cancer and two from tuberculosis. These two population surveys appear to imply that the risk of cancer from all solitary circumscribed pulmonary nodules is not very great; the retrospective studies of resected nodules show clearly that it is a different story when an experienced physician or surgeon decides, by reason of its size, appearance, associated symptoms, or any other consideration, that resection of a nodule is indicated.

From available sources in the literature, a compilation has been made of the surgically proven causes of solitary circumscribed lung metastasis.[1,3,5,10,11,18,19,29,32-34] These are recorded in Table 4. The commonest primary sites of these solitary metastases are the colon, kidney, breast (Fig. 9), testicle, female generative organs, nose and throat, bone, and melanoma, in that order. Other primary foci have been relatively infrequent and are also listed in Table 4.

Comment

From a review of the literature and from our personal experience, certain clinical features of the solitary circumscribed pulmonary nodule appear worthy of emphasis. It is clear that roentgenographic evidence of calcium in such a lesion greatly reduces the chance of its being malignant (Fig. 10). Unfortunately, however, the presence of a small amount of apparently calcific density

TABLE 4.—*Solitary Circumscribed Lung Metastases Proven Surgically from Literature*

	No.		No.
Colon	16	Thymus	1
Kidney	12	Prostate	1
Uterus and ovary	9	Liposarcoma	1
Breast	8	Synovium	1
Testicle	6	Larynx	1
Pharynx	6	Bronchus	1
Melanoma	3	Adrenal	1
Bone	3	Salivary gland	1
Thyroid	2		
		Total	72

Fig. 9.—Solitary metastasis of breast carcinoma. A 42-year-old woman had a radical mastectomy for carcinoma of the left breast in 1949; skin recurrences were removed locally in 1953 and 1954. A 1.5 cm. nodule in the right upper lobe was noted in July, 1956, which had not been present six months before. Illustrated is a tomogram taken at the same time. It was removed by wedge resection in August, 1956.

does not exclude malignancy. As a matter of fact, calcification may be seen not only in tuberculosis, coccidioidomycosis, histoplasmosis, hamartoma, and hematoma, but also in foreign bodies, parasitic infestations, metastatic osteogenic sarcoma, and, rarely, bronchial adenoma.[35] The coexistence of calcium and cancer has recently been documented by Davis et al., who found surgically proven malignancy in 155 cases with such a preoperative roentgenographic appearance in a recent survey of thoracic surgeons through the United States.[36] The interpretation of calcium in the chest roentgenogram is a source of some disagreement, thus opening this report to some debate. The fact remains, however, that calcium was actually found by the pathologist in intimate association with the tumor in some of these cases. It is also a fact that calcium is too often interpreted when the roentgenographic evidence is uncertain. Tomograms may be helpful in being sure about the presence of calcium.

Total calcification (Fig. 11) or the presence of concentric laminations (Fig. 12) is indicative of an inflammatory origin. The laminations appear to be due to repeated healing and local progression of the process and are usually due to histoplasmosis. The presence of spicules radiating from the lesion (Fig. 13) is indicative of malignancy;

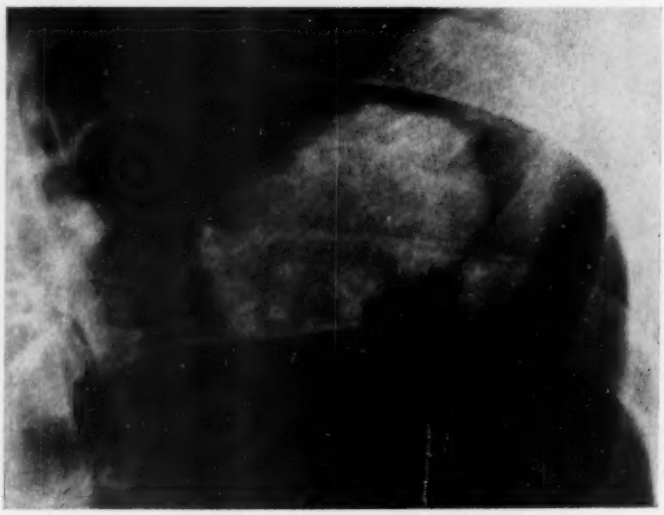


Fig. 10.—Partially calcified tuberculoma. A 60-year-old man was given bed rest for two years for left upper-lobe pulmonary tuberculosis in 1936-1938. A new lesion appeared in the superior segment of the left lower lobe in 1941. After increasing slowly in size for five years, this shadow remained unchanged in size and calcification became evident. After the patient lost 20 lb. and had left pleurisy for two months, a chest roentgenogram in May, 1956, (shown here) revealed a partly calcific and unbilicated 3×4 cm. mass in the superior segment of the left lower lobe. Segmental resection in June 1956, revealed a thick-walled cavity filled with thick cheesy pus containing numerous tubercle bacilli.

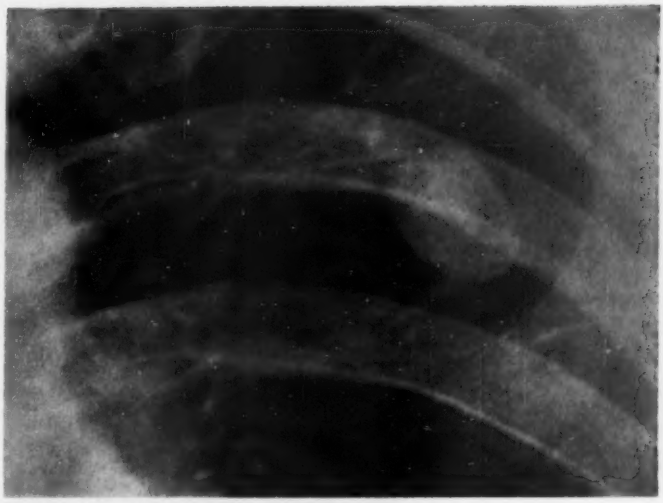


Fig. 11.—Totally calcified tuberculoma. A 43-year-old man received left pneumothorax for three years following the discovery in 1932 of a cavity in the left upper lobe and acid-fast bacilli in his sputum. In January, 1947, about 15 years later, the 2.5×3.5 cm. nodule had the appearance seen here. In August, 1950, the patient died from bronchogenic carcinoma. On examination the tuberculoma was "completely healed" morphologically and no tubercle bacilli were found.

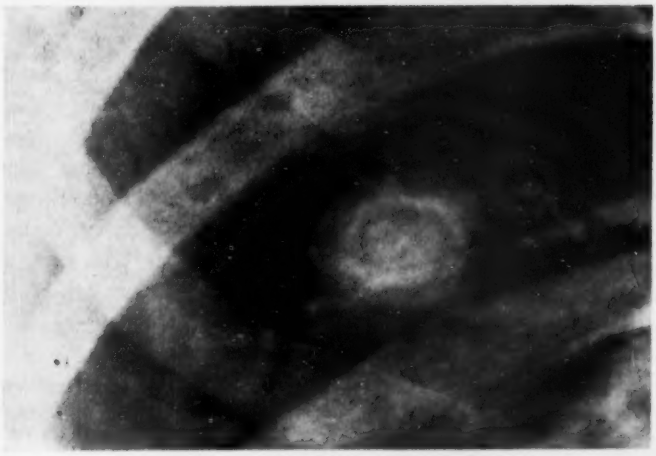


Fig. 12.—Laminations in histoplasmoma. A 45-year-old man was found to have a nodule in the right lower lobe in 1945. Serial films revealed a slow increase in size. Its appearance in January, 1954, measuring 2.0×2.5 cm. in diameter, is shown here. PPD No. 1, histoplasmin, and coccidioidin skin tests were positive. Wedge resection was performed in February, 1954.

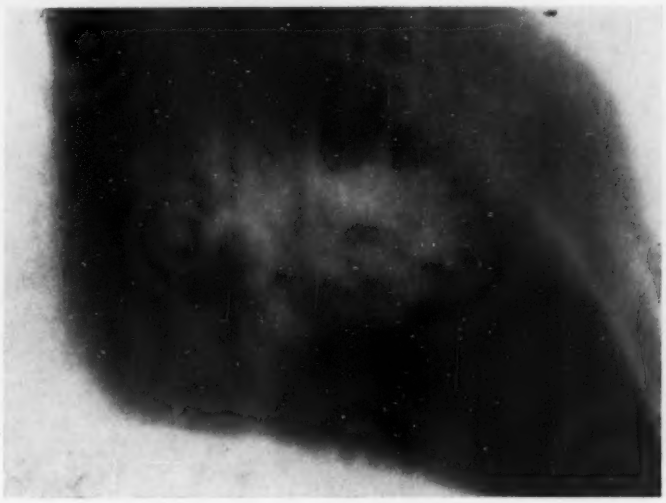


Fig. 13.—Adenocarcinoma with spicular radiations. A 45-year-old man complained of chest pain and hemoptysis for two months. The tomogram taken in March, 1956, and shown here revealed a nodule of 3×4 cm., with spicules radiating from it in the left lower lobe. He had a left pneumonectomy in March, 1956. Metastases to hilar lymph nodes were found.

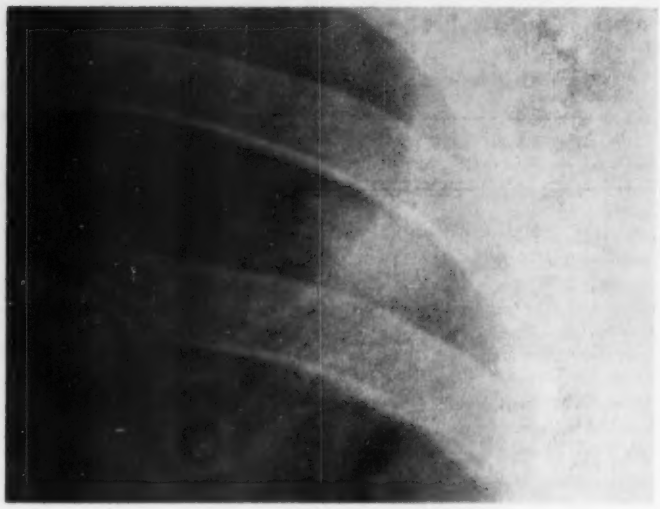


Fig. 14.—Histoplasmoma with "daughter" lesions. A 48-year-old man had a negative routine chest roentgenogram in November, 1951. After intermittent left pleuritic pain for five months a film in June, 1952, revealed a 1 cm. nodule in the left midlung. One taken in October, 1952, is shown here. PPD No. 1, histoplasmin, and coccidioidin skin tests were positive. The nodule, after removal by wedge resection in October, 1952, revealed Histoplasma capsulatum on section.

they appear to represent local lymphogenous extensions of the malignant process.

The preexistence of cavity within the nodule increases the chance that the lesion is inflammatory, but unfortunately it does not eliminate malignancy.

Location of the lesion may be helpful in that infectious granulomas are usually within a few millimeters of the periphery of the lung, including the lobar septa, whereas malignancies are frequently more central in location.

The presence of associated "daughter" lesions (Fig. 14) very significantly raises the chance of an infectious origin. In fact, the authors have yet to see a nodule with "daughter" lesions nearby due to malignancy and have yet to find such a report in the literature.

The presence of umbilication on the surface of a circumscribed nodule is supposed to increase the likelihood of malignancy (Fig. 15).[37] Exceptions to this observation,

Fig. 15.—Adenocarcinoma with umbilication. A 32-year-old woman complained of dry cough for many years, with yellowish blood-streaked sputum for six months. A chest roentgenogram in February, 1953, shown here revealed a 3 cm. round mass in the right lower lobe. PPD No. 1 and 2, histoplasmin, and coccidioidin skin tests were negative. Right lower lobectomy was performed one month later. She died of metastatic carcinoma three years later.

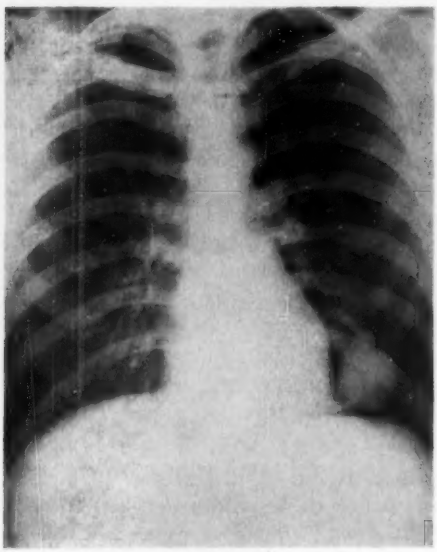


Fig. 16.—Congenital ectatic vein with umbilication. A 25-year-old man without symptoms had a routine chest roentgenogram (shown here) taken in December, 1943. The 4×5 cm. mass was definitely umbilicated on is lateral margin. Left lower lobectomy in March, 1944, revealed a congenital ectatic vein.

however, may occur (Fig. 16), especially due to tuberculosis and hamartoma.

Changes in the size, shape, or appearance of the nodule in serial roentgenograms should be helpful but in actual practice are not. Customarily a malignant nodule enlarges, often rapidly. It is well documented that malignant nodules have remained unchanged over periods of 12 months and longer. On the other hand, a granuloma may visibly shrink or enlarge during a similar or even shorter period.

The age of the patient may be most helpful in these cases; a nodule in a person below 35 years of age has only a small risk of being due to malignancy, whereas those in persons over 35 have an increasing risk of malignant origin as the age rises to 60. Twelve per cent of the 145 cases of bronchogenic carcinoma seen between 1947-1955 at Fitzsimons Army Hospital were 34 years old or younger.

As regards sex, not only is lung cancer much less frequent in females, but also nodules of all kinds seem to occur in them less frequently than in males.[30-32]

The presence and character of symptoms appears to be fairly helpful in distinguishing malignant from nonmalignant nodules. This is particularly true of pain, hemoptysis, chronic cough, and recurrent pneumonitis. While the absence of symptoms does not by any means exclude cancer, it appears to reduce the chance of it.

Skin tests and fungus complement-fixation reactions are always part of the evalua-

Fig. 17.—Coccidioma. A 22-year-old man had a chest roentgenogram following an upper respiratory infection in February, 1956. A tomogram taken at the same time is reproduced here. PPD No. 1 and histoplasmin skin tests were negative; PPD No. 2 and coccidioidin tests were positive. Coccidioidal complement-fixation test was negative. The 1.5×2.0 cm. mass in the right upper lobe was removed by segmental resection in March, 1956.

tion of these patients but are not as useful as one would desire. Cancer may obviously exist in the presence or absence of tuberculin hypersensitivity; the same is true of the fungus skin and serological tests. Unfortunately, also, histoplasmin or coccidioidin hypersensitivity and positive complement-fixation tests do not prove that a pulmonary nodule is caused by histoplasmosis or coccidioidomycosis (Fig. 17), respectively; nor is the reverse true, that these conditions can be reliably excluded by virtue of negative skin and complement-fixation reactions.[38] The skin and complement-fixation tests, in other words, are helpful but not diagnostic in these cases.

The adherence of traces of these antigens to syringes and needles despite washing, boiling, or autoclaving may be responsible for occasional false-positive skin reactions. The antigen can be removed by soaking in dichromate solution. It is best to label and use each syringe and needle for one of the three tests only.

Geography may be an aid in the diagnosis of these lesions. The attitude toward these nodules, particularly in the Southwestern United States, where coccidioidomycosis (Fig. 17) is endemic, is quite different than elsewhere in this country. Histoplasmosis is considerably more widespread than coccidioidomycosis but is concentrated in the Mississippi and Ohio River valleys. There is no indication to date that removal of either a histoplasmoma or coccidioma is indicated. Even in the endemic areas, unfortunately, there appears to be no truly reliable way of making these diagnoses with complete confidence.

Bronchoscopy may be helpful, especially in securing material for cytological examination; as one might expect from the peripheral location of these lesions, cytological examinations are negative in 80% or more of such cases, and bronchoscopic abnormalities are very rarely seen.

The bronchogram is rarely helpful in the diagnosis of these lesions.

Competent sputum, gastric, and bronchial-washing bacteriology may be diagnostic. A specimen for fungus culture examination must be inoculated while it is quite fresh or it is very apt to be worthless. If tubercle bacilli are found in sputum or gastric washings the risk of cancer is greatly reduced but again not excluded, because cancer and tuberculosis may coexist, (Fig. 11).[39]

The benign behavior of solitary nodules of proven tuberculosis origin is worthy of reemphasis. Far from being the "time bombs" they were once thought to be, numerous reports have established that these lesions[6,40-50] are as benign a form of pulmonary tuberculosis as there is. Relapse has occurred in from 20% to 25% in 5-20 years after therapy with rest or pneumothorax and without surgery or chemotherapy. Relapse was seldom severe, and death from tuberculosis very rare. This experience is more favorable than with minimal pulmonary tuberculosis.[51]

Bacteriologic and pathologic examination of a resected granuloma frequently left the etiology in doubt. In recent years, especially with the use of periodic acid-Schiff (PAS) stain,[52-53] a fungus etiology has been established with increasing frequency, especially in the endemic areas of these diseases.

The possibility of saving a life by removing a bronchogenic carcinoma when it is in the stage of solitary circumscribed pulmonary nodule must once again be emphasized. Exploratory thoracotomy carries with it today an operative mortality of less than 1%. There is no doubt that five-year and longer "cures" of proven solitary nodular cancer have been documented; furthermore, the chance of cure is apparently greater when pulmonary cancer presents as a solitary nodule than when it is in one of its more conventional forms. Unfortunately, too many primary nodular cancers still prove to be inoperable or operation fails because of metastasis.

When the chance of having cancer is as low as 2% or 3% in a person and when one can expect no more than a third of these

to be cured, the chance of saving a life with such an operation is no greater than the operative risk. When the chance of a nodule being cancer appears to be 5% or more, the chance of being able to perform curative surgery outweighs the operative risk.

Summary and Conclusions

A heterogeneous group of 1423 patients with solitary circumscribed pulmonary nodules collected from the literature were proven by operation to have had primary or metastatic malignancy in 39%. Forty per cent were found to have granulomas, mostly tuberculous or of unknown cause; thirteen per cent had benign tumors; eight per cent had other benign and essentially nonclinical causes.

By contrast, in a recent survey of 666 patients with solitary circumscribed noncalcified pulmonary nodules Holin and associates found only 3% with proven malignancy over a five-year observation period, 1949-1954.

Bronchogenic carcinoma may present itself as a solitary circumscribed pulmonary nodule; if removed at this stage it can sometimes be cured.

Exploratory thoracotomy is a reasonably safe operation, with a mortality risk of less than 1%.

Certain features of the solitary circumscribed pulmonary nodule of unproven etiology tend to favor open thoracotomy: age above 35, diameter of 2 cm. or more, central location, the absence of calcific densities within the nodule, the presence of symptoms probably referable to the nodule, and the absence of a demonstrable cause other than cancer.

Certain other features tend to reduce the indication for removal in such cases: age under 35, the female sex, diameter of less than 2 cm., the presence of calcium in the nodule, especially if totally calcified or if laminated, the presence of daughter lesions nearby, and the absence of any associated symptoms.

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Pathological Changes Noted in Bone Marrow in a Case of Q Fever

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The known pathological changes in Q fever are sparse and relatively nonspecific. The most conspicuous pathological findings are confined to the lung,[1] and, although recently granulomas have been described in the liver,[2] in general other organs show even less specific findings.

In a fatal case of Q fever the bone marrow has been described as showing an increase in fat and a depression of the myeloid element,[3] while in another case it was found to have a relatively normal erythromyelopoietic series.[1] Lillie et al. have described small nodules of lymphocytes and "vague nodules of epithelioid cells and fragmenting leukocytes in the splenic pulp and bone marrow of monkeys."[1]

Recently, in sections made from a bone marrow clot in a case of Q fever, the authors encountered changes believed to be an angiitis.

Report of a Case

A 32-year-old white man entered the hospital on Feb. 20, 1956, with a history of an abrupt onset of fever and generalized malaise 13 days prior to admission. The patient stated that he had consulted a local physician soon after the appearance of the symptoms and the case had been diagnosed as malaria. On admission there was no history of rash, petechiae, or tender points on the finger tips; no swollen glands, cough, or chest pain, although there had been some vague pain in the lower lumbar region. The patient's only contact with animals had been with his dog. There was no history of exposure to contaminated water or unpasteurized milk. In 1947 the patient had had a documented attack of malaria. Since 1947 he has had approximately one febrile episode a year, which episodes were attributed to recurrences of malaria, although no organisms had ever been demonstrated again in blood smears.

Physical Examination.—Physical examination on admission revealed a slender well-developed young man. There was telangiectasia over the upper sternal area and across the shoulders. There was no significant lymphadenopathy. The pulse was 80 and regular; the blood pressure was 110/85. The lungs were clear; the liver and spleen were not palpable. The temperature was 101 F. The back had a normal contour, and, except for a slight tenderness at the level of the lumbosacral articulation, the physical examination was completely normal.

Laboratory Studies.—Laboratory studies revealed the patient to have a WBC of 15,000, with 73% polymorphonuclear leukocytes, 24% lymphocytes, 1% monocytes, and 3% eosinophils. The hemoglobin was 13.3 gm. per 100 cc.; the hematocrit reading, 44%, and the serology, negative. The total protein was 5.6 gm. per 100 cc., with 3.8 gm. of albumin and 1.8 gm. of globulin. Negative results were obtained on febrile agglutinations, cold and heterophil agglutinations, second-glass urine specimen, three blood cultures, coccidioiden skin test 1:100 and 1:10, and a thick-and-thin smear for malaria. Second-strength PPD skin test was equivocally positive in 48 hours. The urinalysis and serum chlorides were within normal limits. On March 1, 1956, a blood specimen was sent to the Public Health Laboratory in Berkeley, Calif., for a complement fixation for "Q" fever, which was reported as 1:64. On March 26, 1956, another sample was taken, and this was reported by the same laboratory as 1:128. X-ray of the chest and an intravenous pyelogram were negative.

Course.—On entry into the hospital the patient had a temperature of 101 F and for the first week ran a daily temperature with spikes as high as 103 F. The following week the temperature descended to an average of 100 to 100.5 F daily, and by the fourth week in the hospital the patient was completely afebrile. On Feb. 29, 1956, in a search for granulomata, the patient had a bone marrow aspiration from which smears were made,

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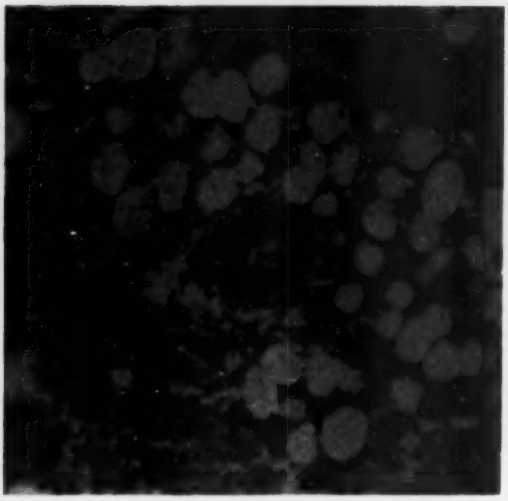

Fig. 1.—Photomicrograph showing broadening of the wall of the vessel and narrowing of the lumen.

and the bone marrow blood clot was sectioned for histological examination. Examination of these sections revealed that several of the vessels had broadened walls with intimal proliferation. Some of the vessels appeared to have a markedly narrowed lumen (Figs. 1 and 2). Infiltrated throughout the walls and in the perivascular areas were lymphocytes, monocytes, and some neutrophilic granulocytes. There was a piling up of similar inflammatory cells within the lumen, which amounted almost to occlusion in some instances (Figs. 3 and 4). The remainder of the marrow had a normal erythromyelopoietic series, and no other abnormalities were noted.

On March 5, 1956, the patient's left knee became swollen, tender, and warm; this condition persisted for several days. The synovial membranes appeared to be markedly tender, and there was a definite limitation of all movement. In connection with this episode the antistreptolysin titer was 50 Todd units; two blood smear preparations for L. E. cells were negative, and throat cultures grew out pneumococci. Examination of prostatic fluid revealed no WBC or organisms, and the culture was sterile. Serum uric acid was 1.8 mg. per 100 cc.

On symptomatic therapy alone the patient gradually improved and at the time of discharge felt well except for a slight degree of weakness.

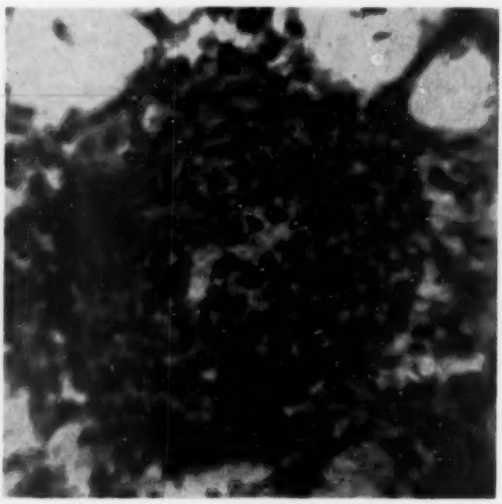

Fig. 2.—Same lesion as Figure 1, with higher magnification.

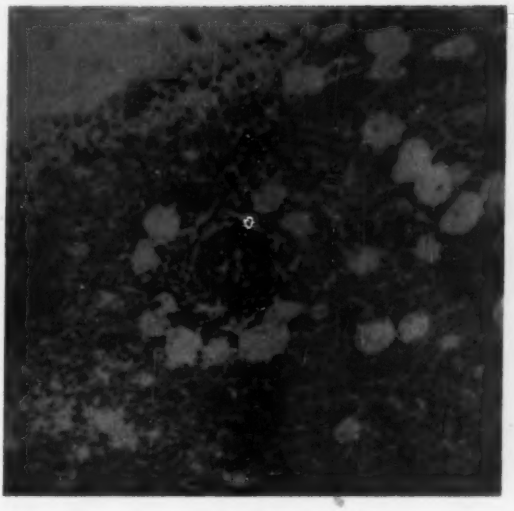

Fig. 3.—Photomicrograph of inflammatory infiltration into wall of vessel and piling up of cells within the lumen.

The patient was readmitted on Aug. 20, 1956, for follow-up studies. In the interval since his previous illness he had felt in excellent health and had gained 20 lb., and his only complaint was that of an occasional low-back pain in the area noted on previous admission. At this time the WBC was 16,250, with 76% polymorphonuclear leukocytes, 19% lymphocytes, 1% monocytes, and 4% eosinophils. Hemoglobin, hematocrit, urinalysis, sedimentation rate, serological studies, total protein, and albumin-globulin ratio were all within normal limits. X-rays of the chest were negative. X-rays of the lumbosacral area showed slight narrowing of the interspace between L4 and L5. On Aug. 23, 1956, biopsy of the iliac crest was done, with removal of some adjacent muscle. Sections made both of the bone marrow and of striated muscle revealed no abnormalities. A third specimen for complement fixation for Q fever was taken Aug. 21, 1956, and reported as 1:32. The patient, apparently completely well, was discharged on Aug. 31, 1956.

Comment

The lesion noted in the bone marrow clot was considered by us and other pathologists [4,5] to be an angiitis. Unfortunately for

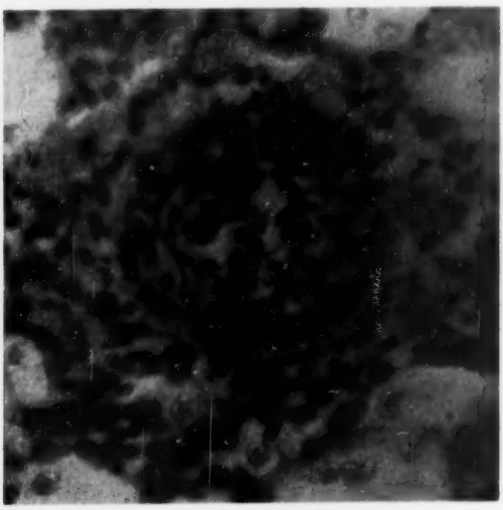

Fig. 4.—Same lesion as Figure 3, with higher magnification.

purposes of verification there were no lesions found on the additional sections on which special stains were done by the Armed Forces Institute of Pathology. Personal communications[4,6] and a search in the literature on Q fever for similar lesions to that described in this case were generally unsuccessful. Some vascular changes have been described in Q fever, such as endothelial proliferation and perivascular infiltration by lymphocytes and plasma cells in the heart of a monkey.[1] In certain unusual cases of bronchopneumonia, which are now believed to have been Q fever,[1] arterial necrosis has been noted.

The lesions described in this case are similar to some of the vascular changes described in rickettsial diseases. Although specific organisms were not demonstrated in this case by special stains, Rickettsia burneti in general has been difficult to demonstrate satisfactorily in either human tissue or that obtained from the experimental monkey.[1,8] The characteristic vasculitis of rickettsial diseases is not usually detected in the bone marrow of typhus,[9] and little note is made in the literature of the bone marrow changes in these diseases.[10,11]

Summary

A case of Q fever is presented in which an angiitis was found in the bone marrow which was consistent with some of the vascular changes described in other rickettsial diseases. Although the possibility exists that these findings may be coincidental, extensive studies on this particular case failed to reveal any other disease except Q fever.

It is suggested that histological sections of bone marrow aspiration material may lend additional information to the knowledge of Q fever and other rickettsial diseases.

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Cholesteremia and Nicotinic Acid

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Introduction

Arteriosclerosis is by far the leading cause of heart disease in old age,[8] although it does not spare the young.[10,13,17] It also offers an increasing problem in psychogeriatrics, largely because of its progressive incidence with senescence and because of increasing longevity.

It is generally accepted that the development of arteriosclerosis is accompanied by, if not due to, a disturbance in the metabolism of lipids. Total cholesterol, cholesterol esters, fatty acids, phospholipids, and lipoproteins have been incriminated singly or again in the ratios or combinations of these variables. However, the general idea seems well established that there is an important relationship between concentration of cholesterol in blood plasma and the development of arteriosclerosis.[11,12] There is also ample experimental, clinical, and histopathological evidence to support the view that a disturbance in cholesterol metabolism is involved in the development of arteriosclerosis.[1]

Although hypercholesterolemia does not necessarily assume a major role in the genesis of arteriosclerosis,[7] it may be indicative of developing atherosclerosis, while the converse does not necessarily hold.

Many approaches have been taken to reduce the cholesterol level in the blood or to exercise arteriosclerotic control: dietary restrictions, hormonal therapy, vitamin B complex, or, again, colloidal stabilizers, such as lecithin and albumen. Recent investigations with the administration of nicotinic acid to rabbits[2] and humans[3,15,16] have stimulated the following investigations.

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The Saskatchewan Hospital.

Method

For the purpose of this study, 45 patients and 2 volunteers were selected. These 47 male subjects were divided into three groups.

Group I.—This group consisted of 27 subjects. Ages ranged from 23 to 60 years, averaging 43.4 years. From a diagnostic viewpoint there were 19 schizophrenics, 2 mental defectives, 1 mental defective with psychosis, 1 epileptic, 1 with traumatic psychosis, 1 manic depressive, and 2 volunteers with no psychiatric disability.

Group II.—Ten patients were chosen at random from cases of psychosis with cerebral arteriosclerosis. Diagnosis was based on the presence of a chronic syndrome characterized by memory loss, periodic confusion, emotional lability, and disorientation. History of a cerebral accident, headaches, dizziness, and signs of peripheral arteriosclerosis, arteriosclerotic retinopathy, and arteriosclerotic heart disease were taken into account. Criteria for onset of illness were (*a*) memory changes (*b*) history of cerebral accident (*c*) onset of periods of confusion. The patients ranged in ages from 56 to 82 years, averaging 67.5 years.

Group III.—This was a control group of 10 patients. Ages ranged from 23 years to 41 years, averaging 33.1 years. In this group there were five schizophrenics, one manic depressive, two epileptics, one epileptic with mental deficiency, and one mental defective.

Procedure

At the beginning of the experiment the fasting total serum cholesterol was determined for each subject by the Sperry-Schoenheimer method. The subjects in Groups I and II were then given 1 gm. of nicotinic acid by mouth three times daily for three months. Group III, the control group, received no medication. One week after and six weeks after the start of the experiment the serum cholesterol levels were again determined. Additional serum cholesterol determinations were made on the patients of Group II at the end of the three months.

Results

The results of these studies are shown in Tables 1 to 3.

TABLE 1.—*Group I: Nonarteriosclerotics*

No.	Total Serum Cholesterol, Mg./100 Cc.				Diagnosis	Age
	Before Nicotinic Acid	During Nicotinic Acid Therapy		Maximal Reduction or Increase		
		After 1 Wk.	After 6 Wk.			
1	245	201	190	—55	Schizophrenia	41
2	180	140	165	—15	Mental defective	42
3	180	115	137.5	—42.5	Schizophrenia	37
4	192	174	178	—17	Schizophrenia	39
5	192	130	159	—33	Schizophrenia	40
6	162.5	175	195	+32.5	Schizophrenia	44
7	154	125	146	+1	Mental defective	45
8	182.5	175	193	+10.5	Epilepsy	60
9	221.5	169	174	—37.5	Traumatic psychosis	51
10	130.5	123	147	+16.5	Schizophrenia	59
11	236	229	267	+31	Schizophrenia	57
12	101	79	79	—22	Schizophrenia	50
13	245	179	155	—90	Mental defective	27
14	288	286	243	—45	Schizophrenia	56
15	200	150	110	—90	Schizophrenia	46
16	472.6	354	190	—282.6	Schizophrenia	46
17	256.7	231.8	233	—22.7	Schizophrenia	56
18	348.2	312.5	297	—51.2	Volunteer	45
19	239	195.5	155	—84	Schizophrenia	31
20	153	155	123	—30	Schizophrenia	34
21	190	145	121.5	—68.5	Schizophrenia	41
22	237	161	166	—71	Volunteer	51
23	239	225	201	—38	Schizophrenia	24
24	165	157	148	—17	Schizophrenia	23
25	200	189	175	—25	Schizophrenia	23
26	189	136	111	—78	Manic depressive	53
27	208	163	149	—59	Schizophrenia	52
Total	5,787.5	4,874.8	4,605	1,182.5		
Mean	214.4	180	170.55	43.9		

Per cent reduction: first estimation, 15.7%; second estimation, 20.4%.

Statistical Analysis of the Data

Group I: (*a*) Changes in mean from before to first estimation, $P<0.001$.

(*b*) Changes in mean from first to second estimation, $P<0.01$.

All changes in the mean are significant.

Group II: (*a*) Changes in mean between before and first estimation, $P<0.001$. Significant.

(*b*) Changes in mean between first and second estimation are not significant.

(*c*) Changes in mean between first and third estimation $P<0.05$. Significant.

Group III: Changes in mean are not significant.

Side-Reactions

Side-reactions consisted of marked flushing and pruritus. These side-reactions on the whole were no greater than those seen after administration of 50 to 100 mg. of nicotinic acid. These reactions diminished and usually disappeared after the first few days of treatment. One patient reported numbness and weakness of the lower limbs as well as flushing and pruritus following the initial doses. These symptoms, however, had disappeared on the second day of administration. It appears highly advisable, therefore, that the patient remain lying down following the initial doses for a period of

TABLE 2.—*Group II: Arteriosclerotics*

No.	Total Cholesterol, Mg./100 Cc.					Diagnosis	Age
	Before Nicotinic Acid	During Nicotinic Acid Therapy			Maximal Reduction or Increase		
		After 1 Wk.	After 6 Wk.	After 12 Wk.			
1	209	124.4	135	132.5	—76.5	Psychosis with cerebral arteriosclerosis	63
2	265	224	225	200	—65.0	Psychosis with cerebral arteriosclerosis	61
3	162.3	136.6	157	105	—57.3	Psychosis with cerebral arteriosclerosis	76
4	248	193	150	221	—37.0	Psychosis with cerebral arteriosclerosis	56
5	235.7	247.5	202	202.5	—33.2	Psychosis with cerebral arteriosclerosis	71
6	264	238	250	179	—85.0	Psychosis with cerebral arteriosclerosis	67
7	190	193.5	184.5	193	+3	Psychosis with cerebral arteriosclerosis	78
8	193.5	153	180	180	—13.5	Psychosis with cerebral arteriosclerosis	59
9	180	193.5	151	180	...	Psychosis with cerebral arteriosclerosis	82
10	288	188	180	180	—180	Psychosis with cerebral arteriosclerosis	62
Total	2,235.5	1,891.5	1,814.5	1,763	472.5		
Mean	223.55	189.45	181.45	176.3	47.25		

Per cent reduction: first estimation, 15.3%; second estimation, 18.8%; third estimation, 21.5%.

TABLE 3.—*Groups III, Controls: Nonarteriosclerotics*

No.	Total Cholesterol, Mg./100 Cc. Start	1 Wk.	6 Wk.	Diagnosis	Age
1	310.5	344	308	Manic depressive	36
2	183	212	214	Epileptic	39
3	275	315	286	Schizophrenic	38
4	237	218	225	Schizophrenic	32
5	216	221	202	Mental defective	23
6	210	234	209	Schizophrenic	23
7	150	153	146	Epileptic	37
8	267	290	295	Epileptic	41
9	166	155	176	Schizophrenic	28
10	209	199	185	Schizophrenic	34
Total	2,214.5	2,341	2,246.5		
Mean	221.45	234.1	224.65		

two hours. Nausea and vomiting occurred in two cases but subsided when the nicotinic acid was taken after meals, their persistence in two other patients necessitated the discontinuation of treatment. One patient in the initial stages of treatment developed extrasystoles; the nicotinic acid was discontinued for four days, and the condition cleared up; resumption of treatment did not cause a recurrence. No side-reactions were noted after the first week of nicotinic acid.

Comment

This limited study, the purpose of which was to supplement the previous work done by Altschul et al.,[3] appears to have confirmed two facts: (*a*) that nicotinic acid does lower the serum cholesterol level, and (*b*) that its lowering action appears to be proportionate to the level of blood cholesterol. The importance of this confirmatory finding lies in the fact that the question can now be asked: Is nicotinic acid in large doses antiatheromatous?

The cholesterol clearing action of nicotinic acid may be twofold: (1) a direct action on the reticuloendothelial system of the liver,[14] i. e., nicotinic acid may increase phagocytosis of cholesterol by reticuloendothelial system cells by speeding up metabolic processes of these cells, (2) an indirect action through its effect on other lipids and/or neutral fats, by which action it would protect the liver in a manner similar to lipotropic factors. According to Boyd[5] (who quotes Gillman and Gillman), "20% of pellagrins in South Africa showed evidence of incipient or frank cirrhosis of the liver" (it would not be presumptuous to assume that in the remaining 80% some liver dysfunction was present). The role of nicotinic acid in causation and treatment of pellagra is fairly well known.

"Hartroft," states Boyd,[5] "has demonstrated in the atheromatous aortas the presence of yellowish-brown pigment apparently identical with the ceroid found in the cirrhotic livers of choline-deficient rats." From the above findings there appears to be some association, therefore, between specific liver dysfunction and atheromatogenesis. The protective activity of the nicotinic acid bears similarity to protective activity of lipotropic factors. It is evident from our study that nicotinic acid does more than lower serum cholesterol. When given to patients with initial low serum cholesterol it tends to increase its level, whereas in cases with high serum cholesterol level it tends, rapidly, to bring it to normal level. It appears therefore to operate as a normalizing, regulating, homeostatic agent. It has been found by Burton[6] that the liver of the normal intact rat is both supplying and removing cholesterol from blood. It is in this function of the liver that nicotinic acid may participate directly (through the reticuloendothelial system) or indirectly (through its protective action).

Approaching the problem from another aspect there is sufficient evidence available of the antilipemic action of heparin, through its participation either in the transport or in the metabolism of fats in man.[4] The question immediately arises whether nicotinic acid is associated with either heparin production or its antilipemic action and what this relationship may be. Does it enhance antilipemic activity of heparin without increasing its anticoagulant property? Boyd[5] states, "I in addition to the level of blood lipids, consideration must be given to the enzyme system in the vessel wall which deal with the lipids . . . the administration of heparin has a remarkable influence in shifting the serum lipoprotein pattern towards

normal—the mast-cell is considered to produce heparin in the body—it may be therefore, that the presence or absence of mast-cells may play some role in the pathogenesis of atherosclerosis; subintimal tissue of blood vessels stain metachromatically with toluidin blue-like tissue which are rich in heparin (mast-cells stain identically)." His statement "that the presence or absence of mast-cells may play some role in the pathogenesis of atherosclerosis" could be enlarged. Mast-cell metabolism may play the role. The inhibition of their metabolism should lead to a decrease in the production of heparin. Thus, any factor interfering with mast-cell metabolism or stimulating the metabolism may be in a similar way causally connected with pathogenesis of atherosclerosis. Nicotinic acid may directly influence the metabolism of the mast cells or may operate indirectly (if its anticholesteremic action is primary) by preventing the accumulation of cholesterol between endothelium and elastica and thus preventing "the suffocation" of mast cells.

These, of course, are hypothetical assumptions—we believe that we are justified to indulge in them, as unbiased search for clues may show a direction for further investigations. The question could be multiplied ad lib., i. e., does nicotinic acid operate as a thyrotropic agent? In what way is it related to thyroid metabolism?"

Is disturbed tyrosine metabolism in the nicotinic acid-deficiency state (pellagra) affecting thyroxin production, and is it the deficiency of nicotinic acid that is primarily responsible for high serum cholesterol in hypothyroidism? Thyroxin also plays a role in the metabolism of calcium; it causes a removal of calcium from the bones, leading to osteoporosis.[18] It seems reasonable, therefore, to query the existence of a relationship between nicotinic acid, thyroid function, and atherosclerosis.

Summary

The study of 47 patients confirmed the cholesterol-reducing property of nicotinic acid. Further studies are suggested to elucidate the role nicotinic acid may play in lipid metabolism and in preventing atheroma formation.

The following people cooperated in this study: P. Sawrenko, Research Laboratory Technician; Mrs. E. M. Fedoroff, Laboratory of Gerontology, University of Saskatchewan, and Dr. A. Hoffer, Director of Psychiatric Research. Nicotinic acid was supplied by Merck & Co., Inc.

The Saskatchewan Hospital.

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Saturnine Gout

A Secondary Type of Gout

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A century has elapsed since Sir Alfred B. Garrod first emphasized the relationship between chronic lead intoxication and the development of gout.[1,2] Many of the early authorities were impressed with this association of diseased states, and the term "saturnine gout" gained wide acceptance. Duckworth [3] states that the first report of coexistent gout and plumbism was made, unknowingly, by Musgrave, in 1703. Brouardel [4] credits Skagge with observing gout in lead workers as early as 1764. Lüthje [5] in 1896, in a very complete review of the literature up to that time lists a number of scattered case reports in which plumbism and gout coexisted. Garrod, himself, in the third edition of his book,[6] acknowledges the priority of others in reporting this concomitance of diseases. However, all subsequent authors agree that it was Garrod who first clearly emphasized the high incidence of plumbism in gouty subjects and suggested a causal relationship. Many observers from various countries confirmed Garrod's observations, and the literature of the latter half of the 19th century is replete with case reports and discussions of saturnine gout. The list of authors contains many of the most illustrious names in medicine of that period. However, there appeared to be great variation in the incidence of this finding in various countries and even in different parts of England, where the condition was found most commonly. Charcot [7] reported the first case from France. Brouardel [4] later stated that he had seen six or seven cases in the hospitals of Paris. Magnus-Levy [8] reported 36 cases of gout, 13 of whom had lead poisoning, while 6 others had undue exposure to lead as painters. Thompson [9] cites 5 cases of gout among 64 patients with plumbism and quotes the claim that gout was present in about half of an early series of patients with lead poisoning seen at The Johns Hopkins Hospital. Hubner [10] described typical gout in lead poisoning. Garrod [2,11] stated that approximately 25% to 33% of the hospitalized patients with gout that he had seen in London were painters or plumbers who had been afflicted with lead toxicity. In large series of patients with gout both Sir Dyce Duckworth [3] and Lorimer [12,13] reported a high incidence of plumbism but somewhat lower than the figures given by Garrod. Numerous other reports of saturnine gout exist in the literature, and we have made no attempt to list all references to this subject.

There was not general agreement among the early authors, however, upon the significance of lead as an etiological agent. Oliver [14,15] and Goadby,[16] in particular, cast doubt upon any direct connection between lead and gout, emphasizing that whereas gout and plumbism were common in the South of England among painters and plumbers it was rare in workers exposed to lead in other industries in the North of England. In Germany, in a region where gout was common, Ebstein [17] found gout in only 9% of a series of more than 1000 patients with lead toxicity. Most authors explained the variable incidence of saturnine gout upon hereditary background for gout and the type of alcoholic beverage consumed in the particular region, and there

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was much controversy as to whether lead acted in a secondary excitant or primary causal manner.

The American literature contains few references to saturnine gout. Packard [18] reported what he thought to be three typical cases, but he believed it to be rare in Philadelphia despite a significant incidence of plumbism at that time.

More recent observers, notably Aub et al.[19,20] have found gout to be a much rarer complication of plumbism than it was formerly thought to be by the early writers. Cantarow and Trumper,[21] in their comprehensive treatise on lead poisoning, state that they have seen only one patient in whom lead may have been an etiological factor in gout. Bauer [22] also attests to the rarity of this combination. Other authorities on gout, notably Talbott [23] question any direct relationship between the two conditions. Two complete reviews [24,25] of the American and English literature on all arthritic diseases covering the period 1940 to 1950 failed to disclose a single case of saturnine gout.

The two patients reported here are of interest in that gout and lead poisoning are associated. In Case 2 gout developed late in the course of chronic lead poisoning, and certain chemical studies performed on this patient suggested a causal relationship between mobilization of lead from skeletal depots and the development of an acute attack of gout, the patient's first in more than two years.

Report of Cases

CASE 1.—A 57-year-old white male house painter was admitted to the men's medical ward at the Hospital of the University of Pennsylvania in February, 1947, with complaints of progressive weakness, heart trouble, and joint trouble. One year prior to this admission he had consulted his physician because he was "all played out." He remembered this mainly as a feeling of weakness and tiredness. In addition he had dyspnea, trepopnea, occasional chest pain, and rare episodes of vertigo. He was found to have auricular fibrillation, with apical rate 180, radial rate 100, no cardiac enlargement, no murmurs, normal ocular fundi, and blood pressure 110/75. After digitalis therapy he reverted to a normal rhythm, but upon stopping the drug of his own volition he again developed auricular fibrillation. From that time he continued to take digitalis in a sporadic fashion. While he was taking digitalis auricular fibrillation was maintained at a controlled rate, and he got along reasonably well until November, 1946, nine months after onset of the original symptoms. At this time he had an episode of congestive heart failure which responded to bed rest and usual therapeutic measures. One month later, and two months prior to this admission, he developed pain radiating down the posterior aspect of the left leg from the sciatic notch to the ankle. The leg felt cold to him, and the pain was partially relieved by heat. No evidence of local circulatory disturbance was found by his physician. The pain lasted approximately 10 days, being so severe as to require opiates, then gradually subsided. At this time the patient noted weakness of the left leg, with "flabbiness of the calf muscles." During the ensuing month, just prior to his admission to this hospital, he noted gradually progressive weakness of the hands, with limitation of finger and wrist motion, both flexion and extension. The left wrist became swollen, without local heat or redness, and he experienced pain in the small joints of the hands. The left ankle became swollen and painful shortly before admission.

System review disclosed that he had lost approximately 40 lb. in weight in the past year and that he perspired more freely than formerly. Deafness, most marked on the right, and slight impairment of vision on the right had been noted over a period of years, perhaps five. In addition to the weakness and dyspnea he had noted marked constipation for approximately four weeks and had recently experienced frequent headaches unrelieved by analgesics.

His past medical history was not remarkable. There was no family history of gout or other familial disease. He had worked for 38 years as a painter, using paint known to contain lead.

On physical examination he was found to be well developed with some evidence of recent weight loss. Blood pressure was 140/90 in both arms; the pulse rate was irregular, 110 at the cardiac apex and 66 at the wrist; temperature and respiration were normal. Excessive perspiration was evident. There was a coarse intention tremor of the fingers. There was decreased hearing on the right, the canals and tympanic membranes being normal bilaterally. The eyes were normal in all respects except for ophthalmoscopic findings. The right optic fundus revealed a markedly pale disk with normal cupping, a degenerative atrophic area in the macula, small retinal vessels with some tortuosity, increased light reflex, A-V crossing changes, but no hemorrhages or exudates. The left fundus was normal except for the slight vessel changes similar to those in

the opposite eye. Nose and throat were normal; no Burtonian line was in evidence. The thyroid was enlarged, firm, and nodular, especially on the right, causing slight deviation of the trachea to the left. There were no abnormal pulmonary findings. Auricular fibrillation was present; but there was no cardiac enlargement, and no murmurs were heard. The abdomen was normal; the left testicle was atrophic; the prostate was slightly enlarged, and a few small inguinal lymph nodes were present. There was a rather coarse tremor of the fingers. Hand grip was weak; there was slight limitation of flexion and more marked limitation of extension of the fingers and wrists bilaterally. The left wrist was swollen, especially in the dorsal aspect. There was limitation of motion of the left hip and the left knee, and left calf muscles were atrophic. All deep reflexes were within normal limits. An area of diminished sensation was present on the outer aspect of the lower third of the left leg. The left ankle was slightly swollen, without local heat or redness. Peripheral pulses were full and equal.

During the course of hospitalization numerous blood cell counts disclosed hemoglobin values varying between 13.7 and 14.3 gm./100 ml. and red blood cell counts, 4,200,000 to 4,700,000 per cubic millimeter, with slight anisocytosis and poikilocytosis. No excessive basophilic stippling was reported, but repeated examinations of peripheral blood smears were not made. Reticulocytes were 1.6% on admission. Leukocyte counts and urinalyses were within normal limits. Blood urea nitrogen was 14, 16, and 9 mg./100 ml; creatinine, 0.9 mg./100 ml.; fasting blood sugar, 92 and 91 mg./100 ml; total serum protein, 6.3 gm./100 ml.; cholesterol, 238 mg./100 ml.; serum calcium, 10.5 mg./100 ml. Serological tests for syphilis were nonreactive. Blood uric acid was the only abnormal chemical finding, being 9.0 and 8.8 mg./100 ml. during the early period of hospitalization.

Roentgenographically the lungs and heart were normal; there was slight widening of the superior mediastinum, with subclavicular extension of the thyroid nodule on the right and with slight deviation of the trachea and esophagus to the left. The hands, wrists, spine, and feet showed no evidence of arthritis; the skull revealed only slight demineralization. Hypertrophic degenerative changes of the right sacroiliac joint and both hip joints, with narrowing of joint spaces, were present. An audiogram demonstrated a 50 db. loss in the right ear throughout the conversational range, with a sudden drop in perception of high tones consistent with typical nerve type deafness. Hearing was normal in the left ear.

Basal metabolic rate was +21; orthodiagram disclosed no cardiac enlargement, and electrocardiogram revealed only auricular fibrillation.

A diagnosis of toxic nodular goiter was made, and the patient was given iodine orally in preparation for thyroidectomy. During this period he developed an exacerbation of joint pain. This was most marked in the hands and left ankle. The pain persisted despite analgesics, until a prompt therapeutic response followed a course of colchicine.

A subtotal thyroidectomy was performed, with removal of a multicystic nodular gland. Postoperatively the patient complained of stiffness and "spasms" of various muscles and had joint pain. All observers agreed that the bizarre muscle and joint symptoms were not typical of tetany. Chvostek and Trousseau signs were lacking, and serum calcium was normal. The muscle "spasms" and pain ceased spontaneously within three days, but joint symptoms remained. Prompt relief was again experienced when colchicine administration was resumed. Auricular fibrillation continued, with the rate controlled by digitalis. Joint symptoms regressed, and a blood uric acid value shortly before discharge from the hospital was 7.0 mg./100 ml.

Since discharge the patient has been followed by his family physician, who has informed us that he has done well except for occasional episodes of dyspnea. His cardiac rhythm reverted to normal and has remained so. No attacks suggestive of gout or stigmata of lead toxicity have ensued. The patient has continued to work as a painter.

Follow-Up Studies Nine Years Later.—Unfortunately, limitation of facilities and technical personnel at the time that the patient was in the hospital precluded quantitative assays of lead in the blood and urine. Therefore an attempt has been made to determine whether there is any evidence of increased absorption of storage of lead nine years after the acute illness which is described above. The results of chemical studies of the blood and urine performed in January, 1956, are as follows: hemoglobin, 13.7 gm./100 ml.; erythrocyte count, 4,310,000 per cubic millimeter; urinary coproporphyrin excretion, 1100μg./24 hours (maximum normal value by method is 300μg./24 hours); blood lead level, 69μg. per 100 ml. (normal value, 30μg. to 50μg./100 ml.); blood uric acid, 4.1 mg./100 ml.

Comment

Although the patient shows no evidence of lead toxicity at present, the above findings suggest that stores of lead remain in the body or that increased absorption of lead is continuing. The blood lead level is but slightly elevated, but the urinary coproporphyrin excretion is significantly elevated. Coproporphyrin excretion serves as a sensitive indicator of heavy-metal toxicity when

other causes of coprophyrinuria can be excluded. It may be elevated when other clinical signs of lead toxicity are absent. In this patient there is no other plausible explanation for the elevated coproporphyrin excretion.

These findings lend support to the diagnosis of lead toxicity suggested during the patient's illness nine years earlier. Many of the clinical features displayed at that time are compatable with plumbism, which may have resulted from mobilization of stored lead due to the hyperthyroidism. He was exposed to lead as a painter for almost 40 years, affording ample opportunity for skeletal storage of lead. Many of his clinical signs were best explained on the basis of mobilization of lead from the skeleton. Dr. Francis H. Adler concurred in the diagnosis of optic atrophy. This was unexplained on any other basis and is recognized to be the most frequently described ophthalmological lesion occurring in lead poisoning.[14,15,19,20,26-29] A neurological consultant concurred in the findings given above and was of the opinion that the patient had a peripheral radicular neuropathy. This is compatible and often characteristic of lead toxicity. The clinical picture was not typical of thyrotoxic myopathy, another diagnosis that was considered. The tremor was different from that usually seen with hyperthyroidism and was characteristic of that which has been described in lead poisoning. Whether or not the nerve type deafness could be attributed to lead is an interesting question. Lead has been known to cause damage to the acoustic or vestibular divisions of the eighth nerve, and it is noteworthy that our Case 2, in whom lead intoxication was proved, had a similar type of nerve deafness. Recently a series of cases of lead poisoning was reported in which a number of patients exhibited hearing loss, with findings by audiogram closely resembling those of our two patients.[30]

As emphasized by Aub et al.[20] many things may promote mobilization of deposited lead, especially factors which predispose to mobilization of calcium. Thyrotoxicosis is conspicuous in this regard. It is our impression that this patient had stored lead in his bones over a period of years, where it had remained dormant, causing no toxic manifestations until mobilized by the development of thyrotoxicosis. In addition the patient was found to have a high blood uric acid level and joint pains exhibiting prompt symptomatic response to colchicine. Joint symptoms were aggravated by surgery and remained so until colchicine was again administered. It is well known that surgery frequently induces acute episodes in a gouty subject. During the course of hospitalization and treatment these symptoms abated, and blood uric acid was found to decline toward a more normal value. As will be discussed more fully below, it appears probable that control of thyrotoxicosis, first with iodine and then with thyroidectomy, removed the stimulus to mobilization of lead and permitted elimination of circulating lead by excretion. The deleterious effect that lead exerts upon nucleoprotein metabolism having been removed, symptoms of gout gradually subsided, and blood uric acid declined toward normal. It is significant that the blood uric acid is now found to be normal.

CASE 2.—A 60-year-old white male machinist was admitted to the Hospital of the University of Pennsylvania in March, 1954, with chief complaint of weakness of his hands. He had been in good health until 1938, when he developed weakness of his hands, with loss of ability to extend at the wrist bilaterally. The patient stated that this was diagnosed as lead poisoning by his physician. He refrained from work for nine months, while receiving medical and electrotherapy. There was slight gradual improvement, which continued after his return to work, but he never regained full strength in his hands.

In 1947 he had an acute attack of pain, involving both great toes, which became hot, red, and swollen, with extension over the dorsum of the foot. All symptoms subsided within one to two weeks. Between 1948 and 1952 he had approximately eight similar episodes, involving one or both feet, with gradual regression in one to two weeks. He had no such attacks in the two years prior to this hospitalization.

On admission he complained that his hands felt swollen and weak, rendering him incapable of tightly closing his fists, extending his fingers, or lifting heavy objects. Numerous other complaints

were elicited, namely, pain in shoulders, low back, elbows, and neck; urinary frequency; constipation; weakness, and insomnia. He had been totally blind in the left eye since 1916 as a result of trauma. Slight deafness had been noted over the past five years. He had had no significant illnesses in the past other than those mentioned. Family history was negative, and careful questioning failed to elicit a history suggestive of gout in any of his family or ancestors.

He had worked for many years in a machine shop where there was known exposure to molten lead and lead dust from a grinding operation. Blood lead levels had been obtained annually by the company medical department for a number of years and had been reported as normal.

Physical findings were moderate obesity and normal temperature, pulse, respiration, and blood pressure (140/95). The left eye was blind, with corneal opacity and early phthisis bulbi, and there was left exotropia secondary to amaurosis of the left eye. The right eye was normal, with no significant changes in fundus, retinal vessels, or optic nerve head. There was bilateral deafness of slight degree. He was edentulous except for six lower teeth, and no lead line was visible in the contiguous gum. Heart, lungs, and abdomen were within normal limits. There was no lymphadenopathy and no edema, and he had adequate peripheral pulses. Bilateral varicose veins were present. There were no tophi. Cranial nerves were normal, except for slight deafness. There was weakness of hands and wrists, with inability to close the fist or extend the fingers completely. There was no foot drop, no sensory changes, or abnormal reflexes.

Laboratory studies were as follows: hemoglobin 91% and 92%, red blood cells, 4,800,000; reticulocytes, 0.2%; no basophilic stippling nor polychromatophilia, and leukocytes, 6900 and 8300, with normal differential counts on both occasions. Blood urea nitrogen was 19 mg./100 ml.; fasting blood sugar, 92 mg./100 ml.; blood uric acid, 8.0 and 8.1 mg./100 ml.; serum calcium, 10.4 mg./100 ml.; serum phosphorus, 2.6 mg./100 ml. Urine: specific gravity, 1.021, with no albumin; 3 to 7 leukocytes per high-power field; no red blood cells; 1 to 2 hyaline casts per high-power field on a typical specimen. Kolmer and Kline tests were negative.

Roentgenographically there were slight hypertrophic changes in the entire spine, pelvis, and distal phalanges. Nothing further abnormal was seen in films of the hands, chest, teeth, or feet, other than bilateral hallux valgus.

Audiograms revealed rather marked loss of ability to hear high tones, with normal perception of low and middle tones. Other otologic tests were interpreted as indicating a nerve type of deafness.

Detailed sensory testing, chronaxic studies, and electromyography were performed. No sensory losses were evident. A number of muscles of hands and feet had elevated chronaxic values (shift of strength-duration curve), and there was decreased sweating over the median nerve distribution on the right.

Electromyograms showed abnormal fasciculation potentials in some of the small muscles of the hands.

The most interesting studies were those relating to lead intoxication. Blood lead level on admission was 0.06 mg./100 ml. and urinary coproporphyrin excretion was 357μg. and 406μg. per 24 hours on two occasions that it was assayed. These findings were interpreted as normal blood lead level and slight elevation of coproporphyrin excretion. At this stage of the diagnostic study there was substantial evidence of neuromuscular damage of lower motor neuron type, confirmed by chronaxic and electromyographic study. The blood uric acid level was elevated, and there was the history of numerous acute episodes suggestive of typical gout. However, none of these attacks had occurred in the previous two years. There were the additional findings of mild degenerative joint changes by x-ray, traumatic blindness of one eye, bilateral nerve type deafness, and bilateral varicose veins of the legs.

For medicolegal reasons as well as for therapeutic considerations it was important to determine, if possible, whether a stored pool of lead existed in the body. Therefore a provocative test with a chelating agent was planned. The results of this procedure will be described below. For technical reasons, however, there was a delay in performing this test. In the interim the blood lead level was again measured on March 19 and found to be elevated to 0.152 mg./100 ml., compared with normal controls (0.06 mg./100 ml. maximum normal blood lead level in our laboratory). Thus the patient's blood lead level had increased to a level more than twice the height of the initial level found at the time of admission to the hospital. On March 24, five days after the elevated blood lead level was obtained, the patient developed an acute attack of typical gout, involving the great toe and the dorsum of the left foot. This attack responded dramatically to colchicine. Another blood lead level, obtained two days after the patient developed the acute gout, was found to be 0.161 mg./100 ml.

The provocative test was carried out March 25 to 29, despite the abundant evidence that lead had been mobilized from body stores. Lead excretion was quantitatively determined in two 24-hour control urine collections. On the third day edathamil calcium-disodium * was administered intravenously

* Administered as Versenate, trade name of Riker Laboratories, Inc., Los Angeles.

in two 1 gm. doses eight hours apart. The urine was collected and assayed for lead during this and the succeeding 24 hours. Edathamil calcium-disodium is a chelating agent with high affinity for the lead ion, with which it forms a poorly dissociated complex which is rapidly excreted in the urine. It is of proved utility in the treatment of lead intoxications.[21-26]

The results of these studies offered further evidence of excess storage of lead in the patient. The control 24-hour urine specimens showed abnormally high levels of lead excretion, 0.250 and 0.370 mg./24 hours, respectively. The maximal normal urinary excretion of lead in adults is usually considered to be 0.1 mg. per day, higher values indicating excess absorption or storage of lead. When edathamil calcium-disodium was administered the urinary lead excretion rose to 0.550 mg./24 hours.

Comment.—It is evident from the laboratory data that the blood lead level increased after the patient was hospitalized and that shortly thereafter he experienced an acute attack of gout, his first in two years. It is pertinent to emphasize that evidence of mobilization of lead was gained before the chelating agent was administered and prior to the attack of acute gout.

The cause of the mobilization of lead could not be identified with certainty. There was no evidence of acidosis, alkalosis, intercurrent infection or fever, or other metabolic disturbance, all of which are known to be capable of causing mobilization of skeletal stores of lead. Although he remained in bed more than was his usual custom, there was no prolonged period of general body immobilization. He was given no medication which could have been instrumental in inducing lead mobilization. The small dose of chelating agent was given only after the latter had occurred. Mild physical therapy, consisting of whirlpool baths to the hands and arms, was administered. However, it is unlikely that the small increment of blood flow to the arms that might have resulted from this therapy would have been sufficient to promote mobilization of stored lead. Another possibility to be considered is that the metabolic changes that precede or accompany an attack of acute gout [28] may have been initiated by the emotional and other stresses coincident with being a patient in a hospital and that these changes facilitated lead mobilization. If such be the case it would be necessary to assume that the metabolic alterations were present at least five days before manifestations of gout appeared, since the blood lead level was found to be elevated at that time. It appears more reasonable to suspect that stored lead was mobilized for some reason which we are unable to specify with certainty and that the acute episode of gout was precipitated as a result of lead toxicity.

Comment

The occurrence of an acute attack of gout after spontaneous elevation of the blood lead level is noteworthy. Bauer [22] states that in the rare cases in which gout occurs with lead poisoning it is probably attributable to the vascular nephritis that accompanies the plumbism. Undoubtedly this may be a factor in some instances, but neither of our cases had evidence of significant renal damage nor sclerotic vascular changes. Neither patient had hypertension. A more plausible explanation in these cases is that nucleoprotein breakdown is accelerated as a result of the toxic properties of the lead ion. The findings of anemia, basophilic stippling, and reticulocytosis, which characterize many cases of plumbism, indicate that there must be an enhanced turnover of nucleoproteins and purines. Krafka [37] has reiterated that any condition that increases maturation rate of red blood cells leads to enhanced uric acid output because the nuclei of increased numbers of immature cells must be extruded and metabolized. Therefore he attributed the association of lead poisoning and gout to the constant anemia present in plumbism. Actually our patients were not anemic, and stippling was not found. It is recognized that significant anemia or stippling evident in peripheral blood smears is not found in all cases of lead toxicity. In retrospect, however, the examinations made in our patients were not sufficient to exclude stippling, as repeated

searches were not made and the bone marrow was not studied. Repeated hemoglobin determinations failed to disclose anemia.

Garrod [2] concluded from his experiments that administration of lead salts resulted in a decreased urinary uric acid excretion, resulting in retention in the blood and subsequent gout. His findings were not confirmed by most other workers.[5,38] Preti [39] actually found increased urinary excretion of purines with lead. These discordant findings might be explained by the findings of Rambousek,[40] who demonstrated elevated purine excretion early in the course of experimental lead poisoning, followed by decreased excretion when renal damage supervened.

In rare instances hyperuricemia and gouty arthritis have been known to occur in association with various diseases involving hematopoiesis, all of which are accompanied by an increased turnover of nucleoprotein. Well-documented cases of gout have been reported in association with polycythemia vera,[41-44] polycythemia secondary to congenital heart disease,[45] chronic leukemia,[46,47] thalassemia,[48] hypersplenism,[49-53] congenital hemolytic anemia,[54-56] pernicious anemia,[57-59] myeloid metaplasia,[60,61] and multiple myeloma.[62] Secondary gout of this nature is admirably discussed by Gutman,[63] who admits that it may occasionally represent a chance occurrence with primary hereditary gout but cites evidence that suggests that such is usually not the case. He points out that the incidence in polycythemia, for example, is higher than could be expected by chance, with involvement of more females than usually seen in the primary type of gout. Furthermore, many authors have pointed out the temporal relationship between acute gouty attacks and treatment of the leukemias with chemotherapeutic agents or irradiation and of pernicious anemia with liver extract. Therapy in such instances is attended by destruction of nuclear substance with release of purines and the end-product uric acid. A large increase in the body's miscible pool of urate, which has been shown to be characteristic of primary gout,[64,65] has been demonstrated, likewise, in leukemia,[66] polycythemia,[45] and myeloid metaplasia.[61] Upon feeding N^{15} glycine to normal man and patients with primary gout, the isotope abundance in urinary uric acid has been shown to reach a maximum in two to four days, the peak being higher and reached earlier in some cases of gout.[67-69] In contrast, a slow progressive accumulation of N^{15}-labeled urate in the urine has been demonstrated in secondary gout accompanying polycythemia [45] and myeloid metaplasia.[61] This suggests a fundamental difference between primary and secondary gout.

It is probable that the two cases of gout reported here and most cases of saturnine gout reported in the past represent examples of secondary gout similar to that occurring in blood dyscrasias. McFadzean and Davis [70] have demonstrated that lead poisoning in both humans and guinea pigs causes appearances of abnormal red cell precursors in the bone marrow, with stippling of normoblasts and erythroblasts. A variable number of these stippled cells show positive iron reaction, often associated with defective hemoglobination of the affected cells. Dustin [71] has presented evidence that the stippled cells of lead toxicity contain ribonucleic acid in the granules. Ribonucleic acid has been shown to be present normally in the basophilic cytoplasmic substance of immature erythrocytes but not in hemoglobinated cells.[72,73] McFadzean and Davis [70] have shown further that the abnormal cells are usually destroyed in the spleen, and thus only a small number are present in the peripheral blood. Splenectomy results in a marked increase of the abnormal stippled cells in the peripheral blood. These studies provide further evidence of the increased erythropoiesis and turnover of purines that accompanies lead poisoning. In this respect plumbism is similar to the diseases of hematopoiesis in which secondary gout sometimes occurs.

No familial incidence of gout was elicited in either of our patients. Whether a genetic predisposition to gout exists in all cases in which secondary gout develops is unknown at present, but evidence such as that cited above suggests that there need not be.

As emphasized by Gutman [63] and others, acute attacks of gout are not well correlated with changes in blood uric acid level, and some precursor of uric acid, or an intermediate, in the synthetic or catabolic cycle of purines may be involved in precipitating acute attacks. Similarly, such a substance could result from the increased turnover of nucleoproteins that accompanies lead toxicity.

There is no denying that saturnine gout has become almost non-existent. This poses the problem of explaining why it was found relatively frequently by the early authorities on gout and plumbism. One might assume that other types of arthritis occurring coincidentally with lead poisoning were diagnosed erroneously as gout, as Bauer [22] suggests. This was undoubtedly true in some instances, but it is difficult to believe that Garrod could have erred in this fashion. It is pertinent to recall that Garrod first demonstrated the hyperuricemia of gout and introduced his memorable "thread test" more than a century ago,[74,75] a pioneer achievement in the application of chemistry to clinical medicine. Furthermore, he clearly distinguished gout from other types of arthritis, for it was he who first proposed the term rheumatoid arthritis.[76] Magnus-Levy,[8] who reported a high incidence of plumbism in gout, also measured the blood uric acid and availed himself of Garrod's thread test to detect hyperuricemia. A high percentage of Lorimer's cases of saturine gout exhibited tophi.[13] Therefore, it appears unlikely that diagnostic errors could be the entire explanation of the higher incidence reported by these early authors.

Oliver [14,15] pointed out that associated lead poisoning and gout were found frequently in the South of England but rarely in the North. Gout is still apparently commoner in the South of England, and it is reasonable to speculate that in Garrod's time, when lead poisoning was much commoner, it could have acted to precipitate overt gouty arthritis in predisposed subjects who had hyperuricemia on a hereditary basis.

It should be emphasized that this report is not intended to imply that saturnine gout is common or that lead is an important etiological agent in gout. It would appear, however, that saturnine gout may deserve to be included with the secondary type of gout, similar to that which occurs with certain diseases of the hematopoietic system where nucleoprotein turnover is increased. Secondary gout is distinctly uncommon in the latter conditions, such as leukemia. An important factor bearing on this is the duration of hyperuricemia or increased production and breakdown of purines. It is probable that most cases of primary gout have hyperuricemia for years before overt manifestations of gout appear. Leukemia and other blood dyscrasias, in which secondary gout has been shown to occur, are usually of relatively short duration and may not afford time for development of gout, except in rare instances. It is likely that this is an important factor in the decreased incidence of saturnine gout. Remarkable advances in public and industrial hygiene have made chronic plumbism a relatively uncommon disease, compared with its incidence in former times. It has been emphasized that many of the cases of lead poisoning seen today occur acutely in children [77]; they do not have lead intoxication long enough to develop hyperuricemia or gout, and it is well recognized that gout of any type is extremely rare before puberty. Many industries have completely eliminated lead hazards, and in those in which it cannot be entirely disposed of workers are watched more closely for evidence of undue lead accumulation and removed from exposure if it occurs. Therefore, chronic plumbism of the advanced type seen by our medical ancestors is much less frequent. This would appear to be the most cogent reason for the

extreme rarity of saturnine gout today, in contrast with former times. The additional factors of errors in diagnosis and chance occurrence of lead poisoning with primary gout probably contributed in some measure to the higher incidence of that bygone era.

It is of interest that our Case 1 has had no episodes suggestive of gouty arthritis since thyroidectomy and that the last blood uric acid level obtained shortly before discharge had declined toward a normal value and apparently has remained there. This is consistent with the hypothesis that hyperthroidism was effective in "deleading" him. With removal of the stimulus to increased nucleoprotein turnover that was provided by the lead, hyperuricemia and secondary gout disappeared. Case 2 has continued to have occasional episodes of acute gouty arthritis. Presumably he still retains some deposited lead, as he has not been treated for any length of time with a chelating agent. Despite the negative familial history of gout, we cannot eliminate with certainty the alternative possibility that he has primary gout with concomitant lead poisoning contributing to make it manifest.

Summary

Two patients presenting evidence of concomitant gout and lead toxicity are reported. In one, gout and plumbism were proved by quantitative lead studies and typical clinical and chemical findings of gout. An acute attack of gout followed closely upon a spontaneous mobilization of stored lead, suggesting a causal relationship between the lead and the attack of gout. In the other patient lead toxicity was not proved by quantitative lead assays, but the history of exposure and the clinical findings are suggestive enough of plumbism to warrant inclusion of this case in this report.

The high incidence of so-called saturnine gout reported in the literature by early authorities on gout and plumbism, contrasted with its extreme rarity today, is commented on. Possible reasons for the reported high incidence in former times are discussed. It is suggested that saturnine gout warrants inclusion with other types of secondary gout, which are likewise rare in occurrence.

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Case Reports

Acute Renal Failure Due to Scleroderma Kidney Disease

A Report of One Case with Autopsy Findings

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The appearance of characteristic renal lesions with marked impairment of renal function is not uncommon in periarteritis nodosa and systemic lupus erythematosus.[1-6] However, in another collagen disorder, scleroderma, the occurrence of a characteristic kidney lesion together with fatal renal insufficiency is not generally recognized and has been reported only recently.[7] The following case illustrates that renal dysfunction may be the only clinical manifestation of visceral scleroderma and that death may result therefrom.

Report of Case

First Admission (April 6 to April 28, 1954).—A 39-year-old white male mechanic supervisor was referred to the hospital for treatment of scleroderma.

About two years prior to admission he developed generalized myalgia associated with painful, swollen, and numb joints of the hands and feet. Tightness of the skin over the hands, feet, and face appeared and was accompanied by inability to close the hands completely or to open the mouth normally. The finger tips turned very pale and sometimes became blue following exposure to cold. There was decreased sweating in the axillary and pedal areas. There was no hoarseness or dysphagia. These signs and symptoms progressed until four months prior to admission, when the patient became aware that his skin was generally thicker. At this time, he received corticotropin (ACTH) therapy of unknown dosage for seven days without benefit. Subsequently, a Trichinella skin test was negative, and a gastrointestinal series was normal. The phenolsulfonphthalein excretion was 40% in one hour. Skull films; glucose tolerance test; electrocardiogram, and serum albumin, globulin, cholesterol, calcium, phosphorus, and alkaline phosphatase were all within normal limits. An intravenous pyelogram was not done because the patient was hypersensitive to both iodopyracet (Diodrast) and sodium acetrizoate (Urokon).

The patient entered the hospital on April 6, 1954, for further evaluation and treatment of this illness.

Physical Examination: Temperature 98 F (oral), pulse 80, respirations 18, blood pressure 120/75.

The patient did not appear ill. The skin was generally smooth and thick, with minimal edema of the hands, legs, feet, and periorbital areas. Ability to flex the fingers and to open the mouth was markedly limited. There was generalized muscle tenderness, as well as some swelling of the joints of the hands and feet. The remainder of the physical examination was unremarkable.

Laboratory Data: The volume of packed red cells, white cell count, differential count, icterus index, and erythrocyte sedimentation rate were all normal. Urinalysis showed a specific gravity of 1.020, acid reaction, no protein or sugar, and no cellular elements. The blood Kahn test for syphilis was negative. The stool guaiac; blood urea nitrogen; fasting blood sugar, and total serum protein, albumin, globulin, creatinine, calcium, phosphorus, uric acid, and alkaline phosphatase were normal. The electrocardiogram, the basal metabolic rate, and the 24-hour urinary 17-ketosteroid excretion were within normal limits. The 24-hour urine creatine and creatinine excretions were 110 mg. and 2400 mg., respectively. Phenolsulfonphthalein excretion totaled 20% in 15 minutes and 53% in 2 hours.

Radiological Studies: Chest film, pharyngogram, and gastrointestinal series were normal. Films of

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both hands revealed no alteration of the bony structure.

Course: Biopsy of the right gastrocnemius muscle revealed normal muscle. Biopsy of the skin of the left wrist revealed changes suggestive of scleroderma. On April 16 therapy with cortisone given orally, 300 mg. per day, was instituted, together with a low-salt diet and potassium supplements. On the 11th day of therapy the cortisone dosage was reduced to 100 mg. per day as a maintenance dose. There was no objective improvement. After 22 days in the hospital the patient was discharged and instructed to return weekly for observation.

Interval History: On May 3, 1954, one week after leaving the hospital, the patient was well, but a week later he complained of a pain in the left chest which was pleuritic in character. Both the physical and the x-ray examinations of the chest were normal. The cortisone dosage was increased to 200 mg. per day for two weeks. This was then reduced to 100 mg. per day until June 9, when it was discontinued because there had been no objective change in his condition. The total cortisone dosage in 55 consecutive days was 9.5 gm. Subsequently, *p*-aminobenzoic acid, 12 gm. per day, was administered orally for 10 days with no effect. This was followed by 4 to 6 gm. of acetylsalicylic acid per day for one week, again with no response. On June 15 there was no change in the physical findings except for an increase in the blood pressure from normal levels to 180/110. The urine on this date revealed a specific gravity of 1.010, acid reaction, trace of protein, no sugar, and no cellular elements. On June 26 the blood pressure was 160/110.

Second Admission (June 29 to July 7, 1954).—The patient reentered the hospital because of progressively severe and constant occipital headache associated with some blurring of vision of two week's duration. There was no nausea or vomiting.

Physical Examination: He appeared chronically ill and was lethargic, but his behavior was rational. The temperature, pulse, and respirations were normal. The blood pressure in each arm was 190/160. The skin changes were the same as those described previously. Examination of the optic fundi revealed slight blurring of both disk margins, with no hemorrhages or exudates. The liver was palpable 3 cm. below the right costal margin, and its edge was sharp and tender. The remainder of the physical examination was unremarkable.

Laboratory Data: The volume of packed red cells, the white cell count, and the differential count were again normal on three occasions. Serial electrocardiograms revealed progressively marked peaking of the T waves. Films of the chest and skull were normal. Blood urea nitrogen, serum potassium determinations, and the results of urinalyses for this admission and the previous one are shown in the Table.

Course: The patient's condition deteriorated rapidly. On the third hospital day the blood pressure rose to 260/140, at which time three successive tonic-clonic convulsions occurred with residual stupor. The convulsions did not recur, although the blood pressure remained elevated to this degree until death. Numerous examinations revealed no change in the optic fundi. On the fourth hospital day the 24-hour urinary output, which previously had been normal, decreased to 1000 ml. Within 24 hours, he was totally anuric. At this time the rectal temperature was 104 F, and signs of patchy consolidation appeared in the right anterior chest. Two days later a pericardial friction rub was heard. Despite vigorous antibiotic therapy and efforts to control the fluid balance, the patient died on the ninth hospital day.

Clinical Summary.—A 39-year-old man first entered the hospital with characteristic findings of scleroderma limited to the skin. At this time he was normotensive and had no evidence of renal dysfunction. He was treated with a total of 9.5 gm. of cortisone over a 55-day period, the last dose having been given 20 days prior to the second admission. He again entered the hospital several months later because of headaches of two weeks' duration, associated with the recent onset of hyper-

Laboratory Data for First and Second Admissions

Date	BUN, Mg./100 Cc.	Serum K^+, mEq./L.	Urinalysis		
			Sp. Gr.	Protein	Microscopic Findings
4/ 7/54	9		1.020	None	Normal
6/15/54			1.010	Trace	Normal
6/30/54	80	4.1	1.013	3+	8-10 RBC; 2-3 WBC; few granular casts
7/ 2/54	128	4.0	1.010	3+	3-5 RBC; 2-3 WBC; few granular casts
7/ 5/54	225	7.2			
7/ 7/54	260	9.2			

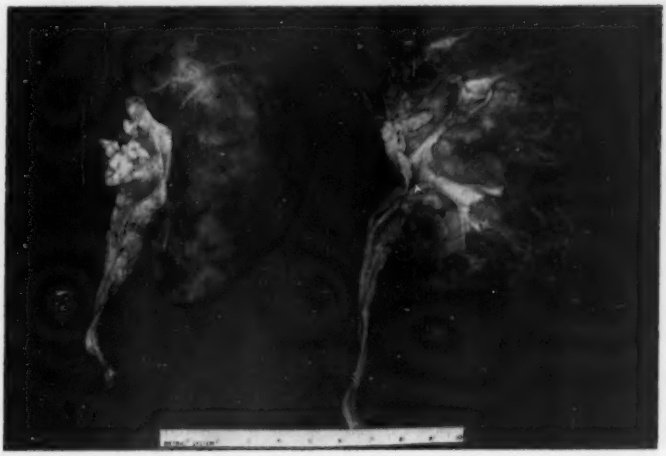

Fig. 1.—Cortical and coronal cut surfaces of the kidneys, showing multiple hemorrhagic and ischemic infarcts.

tension. The course of his illness was then marked by progressive hypertension, sudden anuria, and death in uremia.

Pathologic Findings.—Autopsy afforded a satisfactory anatomic explanation for this man's fulminant renal failure. The normal-sized (140 and 130 gm.) kidneys exhibited a peculiar mottled appearance (Figs. 1 and 2), with irregular and frequently coalescent light brown and dark red hemorrhagic areas, primarily in the cortices. Microscopically these were sites of fresh discrete and confluent necroses indistinguishable from recent infarcts. The lesions were caused by multiple stenoses and occlusions of arteries between the relatively normal arcuate branches and the rarely affected glomerular arterioles. Interlobular arteries showed an advanced form of the concentric loose intimal fibrous proliferation (Fig. 3) described by Moore and Sheehan[7] and Calvert and Owen[21] as virtually pathognomonic for scleroderma. Progression of these lesions with the addition of fibrinoid necrosis (Fig. 3*C*) and thrombosis produced massive cortical necroses. Fibrinoid necroses of glomeruli, afferent arterioles and groups of tubules were confined in nearly every instance to areas of infarction and appeared to be secondary to ischemia. Normal counterparts of these structures were observed in parenchyma that had not been deprived of its blood supply.

Proliferative and fibrinoid vascular lesions like those described in the kidneys were not universally distributed in other organs and tissues. Indeed, the only comparable changes observed elsewhere were limited to the small subcapsular arterioles of each adrenal (Fig. 4).

There was sclerodermatous involvement of the skin. The submucosa and muscularis of the esophagus showed characteristic fibrous replacement.

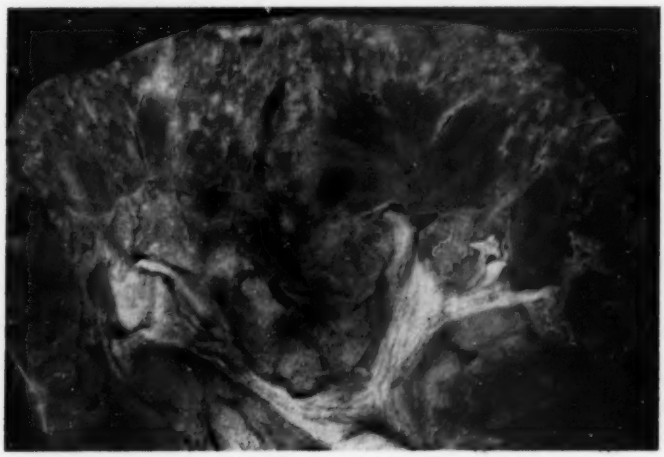

Fig. 2.—Magnified view of left kidney.

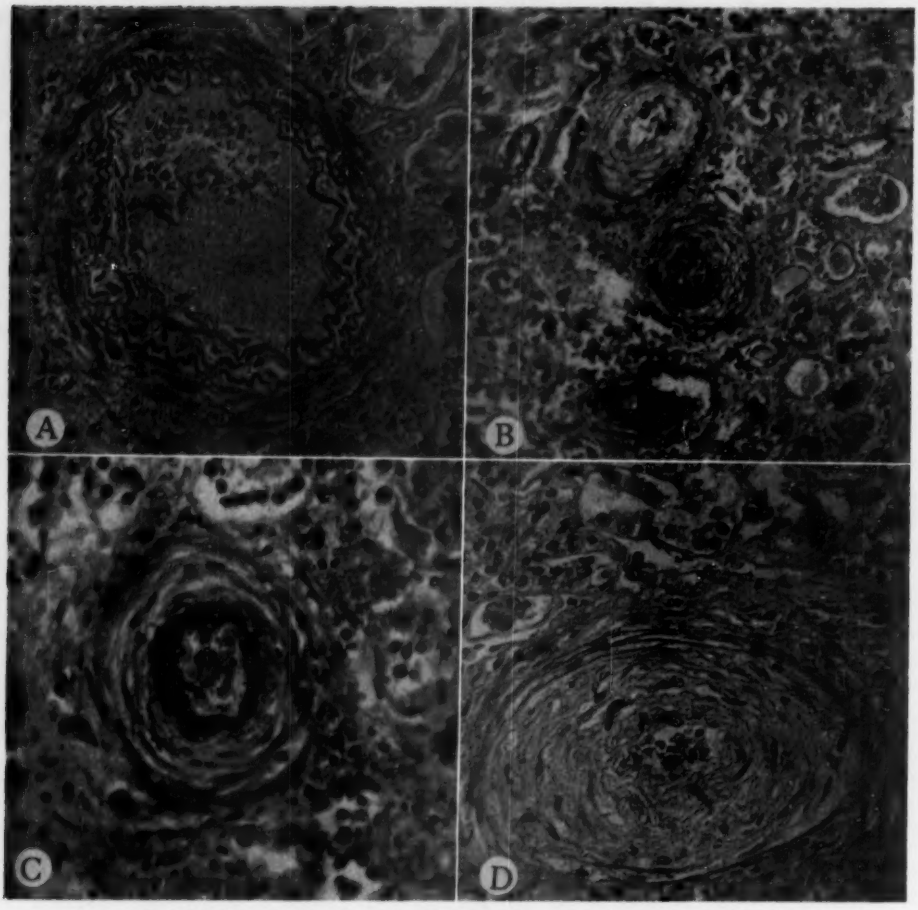

Fig. 3.—Interlobular arteries of renal cortex, showing gradations of occlusive changes. *A*, fragmentation of internal elastic lamella; × 380. *B*, loose intimal fibrous proliferation and sector of fibrinoid necrosis in two vessels at the edge of an infarct; × 128. *C*, intimal fibrosis and fibrinoid necrosis; × 380. *D*, intimal fibrosis with almost complete occlusion; × 380.

This change diminished progressively in the more distal portions of the gastrointestinal tract.

Other anatomic findings were consistent with those of uremia; these included fibrinous pericarditis, scattered serosal hemorrhages, and congestion and edema of the lungs. Widespread bronchopneumonia was the immediate cause of death.

Comment

The present case of scleroderma is unusual because (1) death was due to renal failure; (2) there was associated hypertension, and (3) the kidneys at autopsy revealed gross and microscopic appearances which are now known to be characteristic of scleroderma.[7,10,11,14,17,19,20-22] Although three patients who became anuric terminally are mentioned in a recent abstract,[23] the present case offers the first detailed clinical and pathological description of acute renal shutdown due to characteristic sclerodermatous kidney disease.

Most patients with scleroderma do not have hypertension[7,11,12] or clinically demonstrable kidney disease,[7,9] although the renal arterioles may display varying degrees of intimal thickening.[8,9,12,15] Proteinuria, usually mild, was described in 8 of 15 patients with this disease,[13] but in our experi-

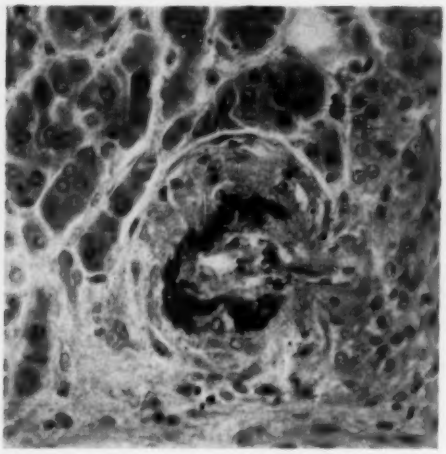

Fig. 4.—Adrenal cortex. Obliterative intimal fibrosis and necrosis in a subcapsular arteriole; × 380.

ence abnormalities of the urine are unusual in scleroderma.

An excellent description of the renal lesions appears in the report by Moore and Sheehan.[7] The pathologic process is a unique lesion in the kidney cortex and consists of marked intimal proliferation of the interlobular arteries together with fibrinoid necrosis of the distal parts of the interlobular arteries and the afferent arterioles. In rabbits with the generalized Shwartzman reaction similar renal lesions have been observed,[16] but the relationship of this observation to the changes in the kidney in man is unknown.

What part corticotropin and/or cortisone therapy may play in the production or aggravation of sclerodermatous kidney disease has not been established. Two of Sheehan's three cases,[18] six of Rodnan's cases,[17] and the one of Banks'[10] were not treated with these agents. In another instance[14] cortisone was given only a few days before the patient died, and it is unlikely that renal failure in this patient and the severe vascular lesions of the kidney that were seen at autopsy were related to this medication. However, cortisone was thought to have been responsible for the acceleration of preexisting renal vascular lesions in Sharnoff's case.[11] It is evident, then, that the renal lesions may occur even though corticotropin and/or cortisone are not used. Whether or not cortisone had anything to do with the fatal outcome in our patient cannot be stated with certainty. This agent was permanently discontinued 20 days before the renal insufficiency developed.

Summary

This is the first description of a case of acute renal shutdown due to characteristic sclerodermatous kidney disease. The typical skin changes of scleroderma were the only abnormalities in our patient until he suddenly developed severe hypertension and renal insufficiency, followed by total anuria and death in uremia. At autopsy the kidneys showed intimal proliferation of the interlobular arteries, together with fibrinoid necrosis of the distal parts of these vessels. It is suggested that these renal lesions may occur even though corticotropin and/or cortisone therapy is not used.

Drs. B. V. Jager, G. T. Perkoff, and M. M. Wintrobe assisted in the preparation of this manuscript.

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Anaplastic Myxoma of Left Atrium

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Despite the fact that primary cardiac tumors have recently become so much less of a medical curiosity that individual cases are being reported less frequently, instances that present interesting and uncommon pathological and clinical features are still worthy of comment. This case of primary myxoma of the left atrium is interesting because of (1) the microscopic picture, which shows a high degree of cellular anaplasia, and (2) its clinical resemblance to coronary artery disease with myocardial infarction, progressive congestive failure, and pulmonary infarction, rather than the customary syndromes of mitral stenosis or embolic phenomena.

In 1942 Beck [1] suggested surgical removal of myxomatous masses, and in 1950, Coulter [2] drew attention to possible removal of such tumors through the atrium if recognized in time. With recent advances in cardiac surgery, such as the atrial well and the extracordial mechanical pumps,[3,4] primary myxoma of the heart becomes a potentially curable lesion. The need for recognition of intracavitary tumors of the heart ante mortem is paramount. A few such cases have been diagnosed ante mortem, all since 1952.[5-7] Bahnson and Newman [6] reported successful removal of a myxoma of the right atrium in which the patient died 24 days postoperatively because of partial obstruction of the inferior vena cava by residual tumor fragments. Steinberg, Dotter, and Glenn [5] reported three cases, in two of which operative removal attempts were unsuccessful. In these cases the diagnosis was made largely with help of angiocardiography and cardiac catheterization. At the February, 1957, meeting of the Pacific Coast Surgical Association, Robertson [8] described the successful removal of a myxoma from the left atrium. This tumor had a long pedicle and was removed with relatively little difficulty according to this report. Three additional successful removals of similar tumors by other surgeons were mentioned. However, the case of Likoff et al.[9] is an example of a situation in which, despite cardiac study including catheterization, there was failure to recognize the presence of an intra-atrial tumor preoperatively. Therefore the clinical course of these cases should also be carefully reviewed in an effort to elicit signs and symptoms sufficiently characteristic to help in arriving at antemortem diagnosis.

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Report of Case

A 56-year-old white woman was first seen during the course of a routine physical examination in October, 1950. At that time blood pressure was 120/82 mm. Hg and cardiac examination was entirely negative. Electrocardiogram was within normal limits and there was a mild hypochromic anemia. Two weeks later the patient complained of nevousness and palpitation, for which she was given mild sedation. Two days later she suddenly became extremely dyspneic and orthopneic. Examination revealed tachycardia of 132, blood pressure of 160/100 mm. Hg, and bilateral moist basal rales. A tentative clinical diagnosis of acute congestive failure due to silent myocardial infarction was made. An electrocardiogram showed flattening of T waves in Leads I, II, and V_{4-6} but no suggestive ST segment changes. Complete bedrest was prescribed, and she was given digitalization, low-sodium diet, and sedation. Electrocardiogram five days later showed complete return to normal, which was considered to be against myocardial infarction. She was kept in bed for the next two weeks. During the following two months she complained only of nervous fatigue and palpitations. She again suddenly developed severe

epigastric pain, palpitation, extreme apprehension, dyspnea, and orthopnea, for which she was admitted to the Palo Alto Hospital on Jan. 27, 1951.

Past history revealed excellent health, with no major illnesses, specifically, rheumatic fever.

Physical examination revealed a moderately obese well-developed and well-nourished middle-aged woman appearing very anxious and sitting up in bed without acute respiratory distress. Heart rate was 100 per minute and irregular; respirations, 26; temperature, 97.8 F. Blood pressure was 98/74 mm. Hg. Skin was cool, moist, and slightly pale but without cyanosis. The neck veins were not distended. The lungs were entirely clear. The heart was not enlarged. Heart sounds were distant and of poor quality. Rhythm was totally irregular. At the apex there was a Grade 3 blowing systolic murmur radiating to the left sternal border and to the axilla but best heard in the fourth interspace. The pulmonic second sound was increased. The abdomen was somewhat distended. The liver edge was palpable and slightly tender 2 cm. below the right costal margin. There was no peripheral edema.

There was a mild hypochromic anemia, but white blood cell count, differential count, and sedimentation rate were normal. The electrocardiogram showed auricular fibrillation with a rate of 146 per minute. Precordial leads, as compared with the previous tracings, were strongly suggestive of an anterior myocardial infarction. Presumptive diagnosis of auricular fibrillation due to myocardial ischemia as the result of coronary atherosclerosis was made. It was decided to treat her conservatively without anticoagulants in view of the hepatomegaly. Two days later the patient reverted to sinus rhythm and was much less dyspneic. Chest x-ray showed minimal cardiac enlargement, with dilatation of the aortic arch and minimal congestive changes bilaterally. Electrocardiogram showed elevation of ST segments in Leads II and III and inversion of T waves in Leads III and V_{4-6}. On the next day fibrillation returned but reverted to sinus rhythm on the following day. Electrocardiogram continued to show changes in the T waves and ST segments in the precordial leads, which were consistent with myocardial damage but not entirely diagnostic of anterior myocardial infarction. During this time the sedimentation rate remained normal, as did the white cell count. Hemoglobin value fell further to 9 gm. per 100 cc., and she received two transfusions very slowly.

On Feb. 7, 1951, after two more episodes of change in rhythm, the electrocardiogram was considered diagnostic of anterior myocardial infarction. Later that day she complained of a sharp stabbing pain, aggravated by inspiration and coughing, in the left lower chest posteriorly. For the first time numerous dry rales and a questionable friction rub was heard. There was no evidence of peripheral thrombophlebitis. It was felt that she had had a pulmonary infarction, but because the prothrombin time was 42% anticoagulants were not used. During the next few days the patient continued to fail rapidly, developing cyanosis and dyspnea. X-ray of the chest on Feb. 12, 1951, showed a fan-shaped area of consolidation in the middle left lung field, extending laterally. There was also evidence of smaller areas of consolidation above the right diaphragm, with pleuritic reaction and minimal fluid, sharply demarcated by the transverse fissure. Findings were compatible with left pulmonary infarction and small pleural effusion, with possible pulmonary infarction on the right.

During the next two days she was given nothing by mouth and was fed by hypodermoclysis. Parenteral medication included digitoxin, penicillin, and streptomycin. She developed mild icterus, which rapidly deepened, and on Feb. 13 the icterus index was 128. When the urinary output fell to 600 cc. and NPN rose to 81 mg. per 100 cc. it was felt that she was in hepatorenal failure. However, on the next day her output rose to 1300 cc., the NPN fell to 50 mg., and jaundice was less. She was clinically very improved, and the lung bases were relatively clear. CO_2 combining power was 37 vol.%, and chloride, 470 mg. per 100 cc. On her final day anasarca developed and acute pulmonary edema continually developed and disappeared. She responded temporarily to intravenous aminophylline but finally died.

Discharge diagnosis: (1) anterior myocardial infarction; (2) congestive heart failure and uremia; (3) hepatorenal failure syndrome; (4) pulmonary infarction.

Pertinent Gross Autopsy Findings.—When the pleural cavities were opened, the right lung was found to be completely collapsed, and 3000 cc. of brown fluid was found in the right pleural cavity. This fluid contained large amounts of precipitated fibrin, and there were soft fibrinous adhesions on the surfaces of the parietal and visceral pleura. The right pleural cavity contained 200 cc. of brownish fluid. The heart in situ measured 12 cm. in its transverse diameter, and the chest wall, 26 cm. When the pericardial sac was opened, approximately 100 cc. of clear straw-colored fluid was encountered.

Examination of the Heart: The heart weighed 460 gm. Externally the right ventricle appeared to be dilated and comprised more than one-half the anterior surface of the heart. Examination of the coronary arteries revealed no evidence of thrombosis and no significant narrowing. The arteries showed a minimal degree of atherosclerosis.

Examination of the myocardium revealed it to be normal in color and consistency and to show no evidence of infarct or scarring.

Examination of the right heart showed a rather extensive dilatation of the right ventricle and slight hypertrophy, with the ventricular wall averaging 7 mm. in thickness. The pulmonary and tricuspid valves showed nothing of note. The pulmonary artery was probed for emboli, and none were found in its larger branches.

Left heart. When the left atrium was opened a large tumor mass was encountered, measuring 9.5 cm. in length and approximately 6 cm. in diameter. The mass was oval shaped and attached to the posterior wall of the auricle over a wide area just below the entrance of the pulmonary vein. This tumor mass almost completely filled the left atrium, and it was only with great difficulty that the small finger of the hand could be pushed down along the tumor mass into the mitral valve. The lower pole of the tumor mass lay in the superior margins of the mitral valve. Three-fourths of the diameter of the valve opening was completely filled by the lower pole of the tumor mass. The surface of the mass was smooth, except in two small areas, which appeared to be eroded. The mass was of such size that it had made an impression on the opposite wall of the atrium, to which it was attached. On section the tumor was soft in consistency and uniformly yellow-gray. The foramen ovale was closed (Fig. 1).

Examination of the mitral valve revealed no significant pathological alteration. The left ventricle was normal in size, and the myocardium showed no significant degree of hypertrophy. The aortic valve showed nothing of note.

Lungs: The left lung weighed 600 gm. In the lower portions of the upper lobe there was a large infarct, which was pyramidal in shape and measures 6 cm. at the base. There appeared to be a small area of atelectasis adjacent to the infarct. The posterior portions of the lower lobe showed a rather marked degree of hypostasis. Elsewhere the lung was well aerated and showed no evidence of consolidation. There were no pulmonary emboli or thromboses apparent on gross examination.

Right lung. The right lung weighed 500 gm. It was small in size and was completely airless. Six large infarcts were present in various areas of the lung. There was one infarct in the apex of the upper lobe, two infarcts on the peripheral surface of the middle lobe, and three infarcts in the lower lobe. These infarcts averaged 6 cm. at the base and were pyramidal in shape. Two of the infarcts appeared to be quite old and showed evidence of organization; the other four appeared to be relatively fresh. The remainder of the right lung appeared to be completely atelectatic. No large emboli or thromboses of the vessels were apparent grossly. There was no evidence of consolidation except for the infarcts.

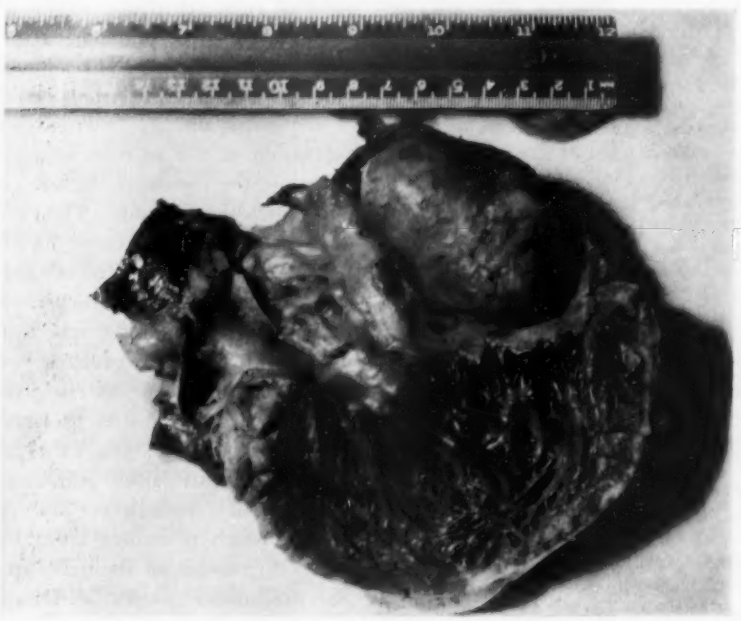

Fig. 1.—Heart. Tumor in left atrium, above mitral valve.

Spleen: The spleen weighed 140 gm. The capsule was slate-gray, and the parenchyma was reddish-purple and moderately soft.

Liver: The liver weighed 1,575 gm. It had a smooth external surface. On section there was an advanced degree of chronic passive congestion, as evidenced by a marked nutmeg appearance. There was no evidence of cirrhosis or of infarcts within the liver.

Microscopic Examination.—Lungs: Sections of the lungs showed multiple areas of relatively recent infarction in which there was evidence of partial hemolysis of erythrocytes in some infarcts and in others of secondary infection. The right lung showed marked atelectasis throughout all lobes and in addition showed evidence of long-standing chronic passive congestion with thickened fibrous interalveolar septa, dilated capillaries, and numerous "heart-failure cells" within the alveolae. Epithelization of the alveolar lining was noted in many areas. The left lung also showed evidence of long-standing chronic passive congestion in addition to the recent infarcts, described above.

Liver: Sections of the liver showed evidence of chronic passive congestion of severe degree and long duration, with marked atrophy of the liver cord cells in the central portions of the lobules and congestion of the dilated sinusoids with blood.

Heart: Sections of the myocardium of the left and right ventricle showed no evidence of significant pathological alteration. There was no evidence of inflammatory alteration, perivascular or otherwise.

Tumor: Sections through the wall of the left atrium in the area of origin of the tumor, described grossly, revealed the tumor to be formed of relatively loose connective tissue containing numerous spindle-shaped and stellate-shaped nuclei. The nuclei showed marked pleomorphism in many areas of the tumor, with relatively frequent mitoses. Many multinucleated giant cells of pleomorphic type were also seen. The stroma stained a bluish-gray on hemotoxylin-and-eosin-prepared sections. The outer surface of the tumor in the area of the erosions described grossly was covered by a layer of fibrin which was free of cellular component. There was no evidence of stratification or layering within the tumor or of hemosiderin deposition. The histology was that of a myxoma of relatively anaplastic variety.

Spleen: Sections of the spleen showed evidence of congestion of the red pulp with erythrocytes.

Sections of the following organs showed no evidence of significant pathological alteration: kidneys, pancreas, gallbladder, adrenals, gastrointestinal tract, uterus, thyroid.

Autopsy Summary.—The left atrium of the heart contained an oval tumor mass which on section had the characteristics of a myxoma of relatively anaplastic variety. The tumor markedly obstructed the mitral valve, resulting in a ball-valve effect. There was evidence of passive congestion of marked degree of lungs and liver with recent pulmonary infarcts, bilateral.

Comment

It is unusual for a primary tumor of the heart to simulate the clinical course of myocardial infarction, although Block's [10] case also suggested this. In our case the electrocardiographic findings were certainly strongly suggestive of anterior myocardial infarction during her final illness. In the earlier phases nonspecific ST- and T-wave changes were seen, indicating transient myocardial ischemia. Even in the later phases of the illness, although the electrocardiographic pattern resembled anterior myocardial infarction, the progression of the pattern was not consistent with development of an anterior infarction. The appearance and disappearance of auricular fibrillation on several occasions, without therapy, was also rather unusual. In the last two electrocardiograms there was evidence of right ventricular strain, which was consistent with the development of massive pulmonary infarction. The pathogenesis of this picture might be explained by some of the gross autopsy findings. There was depression of the anterior wall of the left atrium in the region of the left side of the atrioventricular septum. This could have caused direct compression of the left circumflex coronary artery, simulating a myocardial infarction. In the earlier phases the tumor could have caused myocardial ischemia, due to reduced coronary flow, as the result of intermittent mitral-valve obstruction and coronary ostial pressure. In the final phases of her illness the patient had acute right heart failure with subacute passive hepatic congestion and peripheral edema, which probably helped to promote phlebothrombosis of the veins of the legs, the presumable source of the pulmonary emboli.

Diagnosis of primary myxomas of the heart ante mortem has only been accomplished a few times. Before using angiocardiography or cardiac catheterization this lesion must first be suspected on clinical grounds. One characteristic syndrome is one of multiple peripheral embolic phenomena with vascular occlusion. Thrombi overlying the surface of the tumor may break off and cause emboli to the brain, lungs, aorta, renal arteries, or extremities. Brewin [11] reported occlusion of the abdominal aorta. Steinberg et al.[5] reported cerebral and renal infarction in a case diagnosed ante mortem. Mahaim [12] and Gleason [13] described a syndrome of low-grade fever, rapidly changing murmurs, and embolic phenomena resembling subacute bacterial endocarditis. It is unlikely that any coronary emboli occurred in our case, to simulate myocardial infarction, although this possibility should be considered. A search for such emboli at postmortem examination yielded none.

The commonest clinical syndrome is one resembling mitral stenosis, very well described by Block et al.[10] These cases are characterized by a mitral diastolic murmur due to heart failure, and a rapidly progessive relentless course, intractable to treatment, ensues. If chronic, this may be severe enough to cause right ventricular hypertrophy and pulmonary hypertension. Left atrial enlargement is almost invariably seen roentgenologically, but this is indistinguishable from that of mitral stenosis of rheumatic origin.

The diastolic murmur produced by the ball-valve action of tumors of the left atrium has frequently been described as being affected by shifts in body position. The absence of a history of rheumatic fever is of little value, as suggested by Likoff,[9] because this is seen in at least half the cases of mitral stenosis. Cardiac arrhythmias, especially auricular tachycardia, flutter, and fibrillation, are not uncommonly seen, and this also simulates mitral stenosis.

In summarizing 20 cases reported since 1951, Gleason [13] was not able to obtain any clear-cut clinical picture. However, 13 cases simulated rheumatic mitral stenosis and/or insufficiency, 5 cases suggested subacute bacterial endocarditis, 6 had relentless progressive intractable heart failure, and 4 had Stokes-Adams syncope.

Angiocardiography, which helped Steinberg et al.[5] to diagnose three cases ante mortem, is now the most promising diagnostic tool, since it shows characteristic and persistent filling defects in an enlarged atrium due to intracavitary tumor along the intra-atrial septum. This should certainly be performed in cases of suspected mitral stenosis that show some of the before-mentioned criteria. In a case such as ours, where a myocardial infarction has been suspected, one might hesitate to undertake such a procedure. However, the atypical electrocardiograms, the sudden appearance of the murmurs, and the rapidly progressive intractable heart failure should have aroused suspicions of a myxoma. Only by a high index of suspicion can angiocardiography lead the way to early diagnosis and a possible successful surgical approach.

A second interesting feature of this case is the anaplastic nature of this tumor. In the older literature there is a question as to whether these lesions are tumors or well-organized thrombi. Saphir [15] suggested that sessile or pedunculated lesions in the atrium might be the end-stages of organized thrombi in cases of rheumatic mitral stenosis. Weinstein and Arata [16] reported a case in which they felt the lesion was a thrombus because of associated thickened chordae tendineae. Likoff [9] also felt his case might be a well-organized thrombus.

Mahaim,[12] however, favors classification of myxomas as tumors because of localized proliferation of mucous tissue within the endocardium. Prichard [17] feels that myxomas are a uniform group of tumors with typical pathological appearance; 82% appear in the left atrium, 11% in the right atrium,

Fig. 2.—Microscopic section through area of origin in left atrium (tumor on left, with myocardium on right).

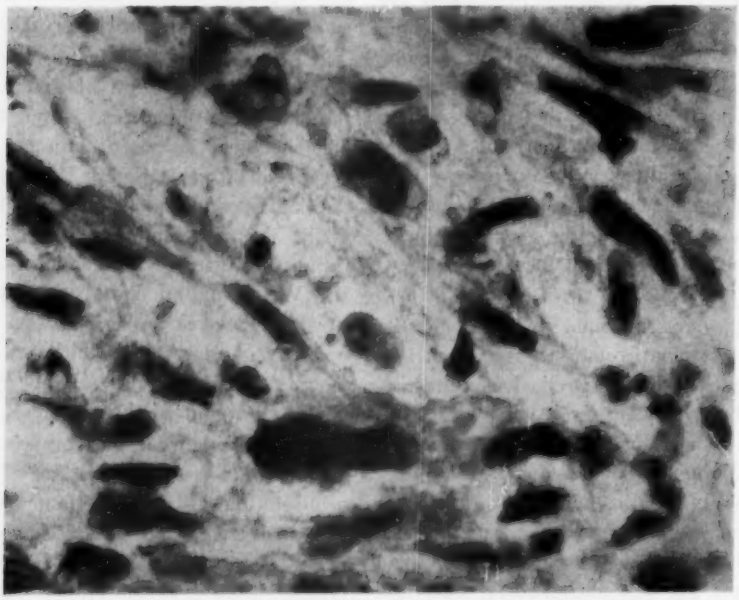

Fig. 3.—High-power magnification, showing cellular pleomorphism and fibrillary stromal tissue.

and 7% in the ventricles. Grossly they are smooth, rounded, or papillary. They are usually pedunculated but may be sessile. On section they are diffusely yellow, soft, and gelatinous. Microscopically they are covered by a single layer of endothelium. The stroma is relatively acellular and contains fusiform and stellate cells with occasional giant-cell forms. The stroma is finely fibrillar. Prichard cites the following points in favor of neoplastic origin: 1. None of these tumors arise in the auricular appendage where thrombi are common. 2. No stratification is seen, which is so common in thrombi. 3. Thrombi contract on organization, whereas these tumors do not. 4. No transitional phase is seen between thrombi and myxoma. 5. There is a predilection for selective sites, such as the fossa ovalis, and valves. The anaplasia of the cellular components of this tumor is most interesting. (Figs. 2 and 3.) In the literature two previous cases have been reported as malignant myxomata. In 1933, Fenster[18] reported such a lesion, but Saphir,[15] in reviewing his paper critically, thought the tumor seen was either a spindle-cell sarcoma or neurosarcoma but not a myxoma. Ringertz,[19] in 1942, also reported a malignant myxoma, but Saphir thought that this was a thrombus giving rise to multiple emboli.

Summary

A case of anaplastic myxoma of the left atrium in a white woman is presented.

The clinical findings simulate coronary vascular insufficiency rather than the usually described mitral stenosis or ball-valve syndrome. The varying manifestations of intra-atrial cardiac tumors assume added importance with recent advances in cardiac diagnostic and surgical techniques.

Though the tumor cytologically is of anaplastic variety, it is sharply demarcated from the myocardium at the site of attachment.

The awareness of this syndrome is no longer only of academic interest in view of recent advances in cardiac diagnostic and surgical techniques, which have recently included successful removal of intracardiac tumors of atrial origin.

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Hepatolenticular Degeneration Associated with Acanthosis Nigricans

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Hepatolenticular degeneration is a relatively rare disease. Its clinical and laboratory features are well known but poorly understood. It was thought desirable to record the findings on this patient in order to report the association of this disease with acanthosis nigricans and to describe this patient's course following treatment.

Report of Case

The patient, a 15-year-old white girl, was admitted to Firmin Desloge Hospital on March 29, 1956, complaining of swelling of her abdomen. She had lived on a Missouri farm and had been in good health until approximately one month prior to admission, when she consulted her family physician because of delay in menarche. At this time she received one injection of chorionic gonadotropin, and shortly she thereafter noticed swelling of her feet and ankles. During the four weeks preceding entry there was a rapid progression of the edema, with a 40 lb. weight gain and development of ascites. She denied any symptoms other than occasional epigastric discomfort, which she thought due to the abdominal swelling. The patient had noticed reddish-orange urine but denied light stools, melena, jaundice, itching, anorexia, nausea, or vomiting. A week prior to entry she had begun to fatigue easily. There was no history of jaundice nor recent association with jaundiced patients. There was no contact with rats or sick animals. Her past history was not remarkable.

No members of her family had liver disease, nor was there knowledge of anyone having symptoms comparable to hers. This was confirmed by interview the parents and the near relatives. In none could brown circumcorneal rings be found. The parents were not consanguineal.

Physical Examination.—On admission blood pressure was 120/70 mm. of Hg; pulse, 90 and regular; respirations, 16 per minute; temperature, 99.4 F orally. The patient was a well-developed young woman, with severe acne over the face, superior trunk, and arms and dark brown pigmentation of the areola and skin folds, most marked in the axilla, where the skin displayed verrucoid changes. The ears, nose, and throat were normal. A moderate icterus of the sclerae was present. On very close examination with oblique lighting a faint yellowish-brown ring (Kayser-Fleischer) could be seen in the periphery of the cornea. This was later confirmed by slit-lamp examination by members of the ophthalmology department.

Examination of the chest showed dullness to percussion and decreased tactile and vocal fremitus over the right inferior posterior thorax. Breath sounds were diminished in this area. The area of cardiac dullness was normal in size; a moderately loud systolic murmur was heard in the second intercostal space to the left of the sternum. The abdomen was protuberant and a fluid wave and shifting dullness were present. The liver and spleen were neither palpable nor ballottable on admission. After the ascites receded the liver and spleen were palpable, but no other masses were noted. The rectal examination was not remarkable. There was a marked pitting edema extending from the feet to the inguinal area. The neurological examination failed to reveal any abnormalities.

The chest x-ray at the time of admission showed an increased density in the lower portion of the right lung field, characteristic of a pleural effusion. X-ray examination of the esophagus failed to reveal evidences of filling irregularity or diverticulum. No varices were noted.

Laboratory Data on Admission.—Urinary pH was 5.5, and the specific gravity was 1.022. The urine tests were positive for bile and urobilinogen but negative for albumin, sugar, acetone, and microscopic abnormalities. The white blood cell count was 7150 per cubic millimeter, with a differential distribution of 2% stabforms 76% segmented neutrophils, 18% lymphocytes, 3% eosinophils, and 1% monocytes. The hemoglobin was 11.2 gm. per 100 cc.; the erythrocyte count, 3,600,000, and the hematocrit, 34 vol.%. The cell indices were normal. The prothrombin activity on the day of admission was 34% of normal.

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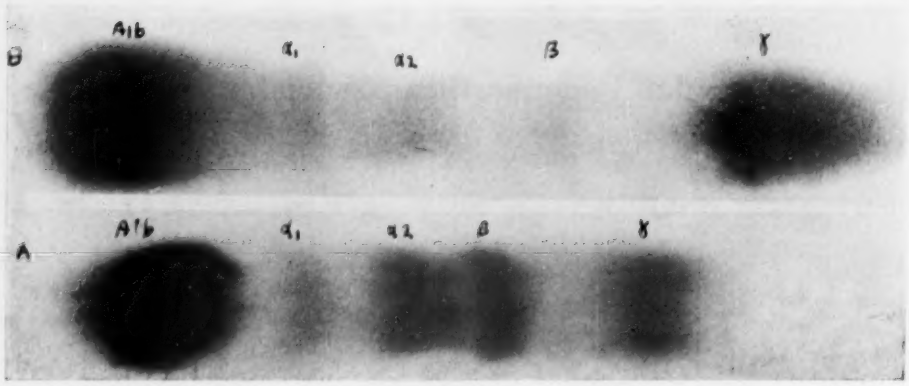

Fig. 1.—Comparison of the electrophoretic pattern in normal serum (*A*) and patient's serum (*B*).

Total serum protein was 5.28 gm. per 100 cc., with 3.13 gm. of albumin and 2.15 gm. of globulin. The paper-strip electrophoretic pattern of serum protein along with a normal is shown in Figure 1. The patient's pattern shows an increase in γ-globulin characteristic of chronic liver disease. The alkaline phosphatase was 3.2σ units. There was 53% retention of sulfobromophthalein (Bromsulphalein) in 30 minutes, 42% retention in 45 minutes. The cephalin flocculation was 4+ in 24 hours. Total serum bilirubin was 3.7 mg., with 1.5 mg. direct-reacting and 2.2 mg. indirect-reacting. The thymol turbidity was 11 units, with positive flocculation. Total serum cholesterol was 132 mg. per 100 cc. Repeated serum amylase determinations were low, ranging from 40 to 80 Somogyi units. The VDRL was negative. A direct Coombs test was negative. The electrolyte values on admission were as follows: sodium, 143 mEq. per liter; potassium, 4.57 mEq., chlorides 124 mEq. Other findings are listed in Tables 1 and 2.

Course in the Hospital.—During this first hospital admission, of four weeks' duration, the patient was maintained on bed rest, a low-salt diet, high-vitamin intake, and mercurial diuretics. Because of the increased amounts of fat in the stool, oral pancreatic enzyme therapy was given in hopes of aiding her nutrition. On April 6, 1956, (eighth day after admission) she was given 1 unit (25 gm.) of serum albumin and 1 unit of whole blood. On April 7 she was given 2 units of serum albumin, following which she had a shaking chill and developed a temperature of 103 F. She rapidly became semicomatose and remained stuporous for three days. Penicillin and streptomycin therapy were begun. On April 9 she was given a second unit of whole blood. The following day there was a rather sudden improvement and the patient became afebrile. Blood, urine, and sputum cultures at the time of the chill and fever were negative. On April 11, after diminution of ascites, the liver became palpable 3 cm. below the right costal margin. The spleen at this time was palpable 3 cm. below the left costal margin. On April 17 neither organ was palpable. With the objective of delaying the progress of hepatic fibrosis, the patient was given 40 mg. of prednisolone daily in divided doses. She continued improving, and the pleural effusion and ascites cleared. Her weight was reduced from 166 lb. on admission to 121 lb. on discharge, April 25, 1956, twenty-six days after entry. At this time the laboratory data were as follows: Urinalysis was negative except for a strongly positive reaction for urobilinogen. The total white blood cell count and the differential were normal. Hematocrit reading was 41 vol.%; hemoglobin, 13.8 gm. per 100 cc.; erythrocyte count 4,000,000. Total serum protein was 6.13 gm. per 100 cc., with 3.02

TABLE 1.—*Stool Analysis*

	Normal	Patient
Total fat, gm./24 hr.	1.8–6.7	21.9
Total fat, % of total stool solid	20–25	57.5
Neutral fat, gm./24 hr.	1–6	12.0
Neutral fat, % of total stool fat	2.5–11	31.6
Nitrogen, gm./24 hr.	1.2	1.1

TABLE 2.—*Results of Special Chemical Analyses* *

	Patient	Normal (Cartwright[10,11])		
		Mean	Standard Deviation	Range
Total serum copper, γ/100 ml.	72	116	±14	68–161
Urine copper, γ/day	960	9	±8.1	0–26
Ceruloplasmin, mg./100 ml.	10.5	34	±4	27–38

*These results were supplied by Dr. G. E. Cartwright, of the University of Utah. On the basis of the above clinical and laboratory findings, the diagnosis of Wilson's disease was made.

TABLE 3.—*Changes in Liver-Function Tests Before, During, and After Dimercaprol Therapy*

Date	Total Protein, Gm./100 Cc.	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Alkaline Phosphatase, Units	Serum Bilirubin (Vandenberg), Mg./100 Cc.			Prothrombin Time, % of Normal	Cephalin-Cholesterol Flocculation	Thymol Turbidity
					Total	Direct	Indirect			
5-16	4.81	2.10	2.71	5.35	1.8	0.8	1.0	33	4+	13 units
5-23*									4+	
5-30	5.91	2.80	3.11	5.25						
6-11†										
6-12	7.91	3.65	4.26	3.85				54		16 units
7-30				4.35	3.0	1.1	1.9		4+	
									4+	
8-28	5.95	2.63	2.32	4.70	3.9	1.4	2.5			

* Dimeraprol therapy started.
† Dimercaprol therapy terminated.

gm. albumin and 3.11 gm. globulin. There was 29% retention of sulfobromophthalein in 45 minutes. The serum bilirubin totaled 1.8 mg. per 100 cc., with 0.8 mg. direct-reacting and 1.0 mg. indirect-reacting. The cephalin flocculation remained 4+ in 24 hours. The prothrombin activity was 27% of normal. The patient was discharged on a regimen of 5 mg. of prednisolone four times daily, potassium chloride, antiacids, pancreatic enzymes, and a low-salt diet.

She was readmitted on May 16, 1956. Since her discharge, on April 25, she had gradually become edematous and her weight had increased from 121 to 138 lb. Physical findings now were essentially the same as those at the time of her first admission, although the edema, ascites, and pleural effusion were less marked.

Laboratory Data.—The findings on urinalysis were negative. The white blood cell count was 6000, with a differential of 57% neutrophils, 37% lymphocytes, 1% eosinophils, 2% basophils, and 3% monocytes. Hemoglobin was 12.7 gm. per 100 cc.; hematocrit, 37 vol.%. Blood-volume studies were within normal limits. Uric acid was 1.9 mg. per 100 cc. Other laboratory values are listed in Table 3.

The patient was given a regimen similar to that of her first admission: low-salt diet, mercurials, and 20 mg. of prednisolone daily in divided doses. The steroids were gradually decreased during her hospital stay. She did not receive intravenous transfusions of whole blood or serum albumin. Despite lack of evidence of central nervous system involvement, it was felt that a trial of dimercaprol (Bal) therapy was warranted in view of the progressive deterioration of her condition. Seven days after admission the patient was started on a course of 1 cc. of 10% dimercaprol solution intramuscularly daily for 20 days. Table 3 shows the changes in liver-function tests before, during, and after this course of therapy.

She was discharged on a regimen of low-salt diet and 250 mg. of edathamil calcium-disodium (Calcium Disodium Versenate) orally four times daily. The last laboratory studies obtained on this patient were on Aug. 28, 1956, five months from the date on which she was first seen. At this time total serum protein was 5.95 gm. per 100 cc., with albumin, 2.63 gm. and globulin, 2.32 gm. It will be noted that this was a considerable decrease in the albumin fraction since the second admission. However, this protein level and albumin fraction were still considerably higher than they had been at the time of her first entry.

She was again seen on Sept. 25, 1956, six months after first admission. There was no edema fluid; her appetite was good, and she was relatively asymptomatic. Skin pigmentation appeared to have lightened. She is to be readmitted for more prolonged dimercaprol therapy.

Comment

During the 44 years since Wilson first described the disorder which bears his name, there has been little added to the clinical picture.[12] However, during recent years great strides have been made toward a discovery of the metabolic abnormalities which are found, notably, defective copper and amino acid metabolism. The role of these defects in the pathogenesis of Wilson's disease has not been established—indeed they may be a result not a cause.

An intake of 2 mg. of copper per day is sufficient to maintain positive balance. The body contains a total of approximately 150 mg. of copper, and much of this is in the liver. Normal plasma copper levels range from 86γ to 161γ, with a mean of 108±9γ,[11, 12] most of which is bound to the α_2-globulin, ceruloplasmin, which has oxidase activity in vitro.[11] This ceruloplasmin copper will react with sodium diethyl dithiocarbonate only after treatment with acid and is referred to as indirect-reacting copper. Most of the re-

maining plasma copper (0 to 17%) is loosely attached to albumin and reacts directly with this reagent.[2] Traces of copper are present in a form which can traverse the renal glomerulus.[4] Normally copper is absorbed from the gastrointestinal tract and is attached to albumin, from which it is rapidly transferred to ceruloplasmin. The route of excretion is the biliary system, with small amounts probably being excreted through the intestinal wall. A distinct pattern of changes in copper metabolism occurs in Wilson's disease. Bush et al.[9] and Bearn and Kunkel,[8] using radiocopper, showed that there was a marked increase in urinary copper excretion and diminution in fecal excretion as compared to that in normal persons. This was true whether the oral or the intravenous route was used. Furthermore these patients have a deficiency of ceruloplasmin,[1,5,11] as a result of which more copper remains attached to albumin, which is reflected in an increased direct-reacting fraction.[8,10,11] Most patients have a hypocupremia, probably resulting from the ceruloplasmin deficiency, although there is little correlation between total serum copper and ceruloplasmin levels.[11]

Most of the patients with Wilson's disease also have amino-aciduria. Many amino acids are excreted in abnormal amounts,[1,6] with threonine and cystine being lost in the largest amounts, and valine, serine, glycine, and others in smaller quantities.[6] Despite the urinary abnormality, the plasma amino acids are normal, and the defective excretion is thought to be a result of a renal lesion which may be associated with copper metabolism. Uzman[7] isolated the urinary copper in a complex with oligopeptides and suggested that the oligopeptides and amino acids are in competition for renal tubular reabsorption, with the resultant massive copper loss.

Pathology.—Cirrhosis of the liver is found in all cases, but, as would be anticipated, the extent of liver involvement varies widely. There is nothing characteristic about the cirrhosis, and it may be either portal or postnecrotic in type.[12] There is often an associated splenomegaly.

The most constant finding in the brain is a symmetrical softening and cystic cavitation in the putamen of the lenticular nucleus. Similar findings may be present in the caudate nucleus, the thalmus, and the cerebral cortex.

The Kayser-Fleischer rings are layers of pigment in Descemet's membrane on the posterior surface of the cornea. As yet no characteristic changes have been described in other organs.

Clinical Features.—Symptoms of liver and brain disease vary widely. There are rare cases in which only hepatic manifestations occur and the patients die in liver failure. It is said that the majority of the patients present with neurological symptoms.[12] However, 7 of Franklin and Bauman's 11 patients had liver disease clinically, and 5 of these had hepatic disease prior to any neurological symptoms. Matthew divides this latter group into those with early onset and those occurring later in life. Children make up the group of early onset and in addition to hepatic diseases present with rapidly progressing rigidity and tremor and eventually become helpless. In the second group tremor begins in early adult life, and it may be the only symptom for years. The majority of the patients have Kayser-Fleischer rings, pathognomonic of the disorder. This is a deposit of golden-brown pigment forming in a 2 mm. ring just internal to the limbus on the posterior surface of the cornea. It is seen in no other condition. Pigmentation of the skin is rare, but occurs.

The subject of this case report falls into that group with evident liver disease and no signs of neurological abnormalities. The delayed menstruation which occasioned her first visit to a doctor is stated by Bearn et al.[12] to be quite often the presenting complaint in a group of young women with chronic liver disease. Pigment changes were present as evidenced by the Kayser-Fleischer rings and skin pigmentation of the verrucous type. Members of the dermatology department considered this to be characteristic of acanthosis nigricans. A photomicrograph of a skin biopsy specimen is shown in Figure 2.

Fig. 2.—Photomicrograph of skin biopsy specimen.

The association of these two conditions in this patient may be coincidental, but it is reported with the thought that future cases of Wilson's disease with skin pigmentation be scrutinized with the characteristics of acanthosis nigricans in mind. In a search of the literature from the past 12 years no case reporting this association came to our attention. It is conceded that although there is no evidence of a malignancy, it may exist, as has been frequently described with acanthosis nigricans. Moreover, the patient's age makes it more likely that she has the juvenile, rather than the adult, form.

Elevated levels of fat in the stool and low values for serum diastase determinations are not ordinarily considered to be characteristic of hepatolenticular degeneration. A low diastase value is often seen in liver disease. It may be that this finding and the steatorrhea are a result of some pancreatic disturbance, although nitrogen content of the stool was normal.

It is difficult to assess the role of a particular therapy in a single case. Improvement during the first hospitalization became striking after intravenous administration of albumin and blood. It may have been that the febrile episode, possibly a reaction from the second administration of albumin, acted as a nonspecific stress stimulus which aided in improvement. However, we considered improvement in protein levels, use of diuretics, and bed rest the most important factors. Prednisolone may have been of some help, but relapse occurred at home while patient was maintained with this steroid.

We were most impressed by the improvement in symptoms, ascites, and blood proteins which occurred after use of dimercaprol during the second hospitalization and would advocate its use in patients with hepatic disease manifestations. Some workers have advocated restricting its use to those with neurological symptoms, since it was only in those in which they had seen a response.

Summary

A case is presented of a 15-year-old girl with Wilson's disease and associated acanthosis nigricans. The clinical and laboratory responses to dimercaprol (Bal), corticoid, and diuretic therapy are outlined.

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High-Output Circulatory Failure Due to Arteriovenous Fistula

Complication of Intervertebral-Disk Surgery

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High-output circulatory failure is an unusual complication of intervertebral-disk operation. Inadvertent injury of great vessels during the operation may result in the formation of an arteriovenous fistula. Circulatory adjustments to the fistula, with the development of high-output circulatory failure, may prompt the patient to seek medical treatment months after the disk operation, at a time when the causal relationship may not be apparent.

Anatomic and surgical features of intervertebral-disk surgery, particularly between the fourth and fifth lumbar vertebrae, predispose to injury of close-lying great vessels. Figure 1 illustrates pertinent anatomy of this area. It is readily appreciated that a small error in placement of a biting instrument, such as the pituitary forceps (the guilty instrument in most cases), might result in injury of the large artery and vein in this area. Laceration of artery alone produces hemorrhage or false-aneurysm formation. Simultaneous injury to artery and vein, however, may result in arteriovenous fistula, since the pressure within the venous bed is lower than that of the surrounding tissues, thus affording a choice runoff for the arterial blood under high pressure.

Signs of vascular injury during the intervertebral-disk operation are frequently overlooked by the anesthetist and surgeon. This contributes to a delayed recognition of the complication. A moderate increase in bleeding, easily controlled, may be the only indication that vascular injury has occurred. This is particularly true if an arteriovenous fistula forms, since the patient then bleeds into his own venous system, concealing the hemorrhage. Because of the paucity of signs, patients may be discharged from the hospital by surgeons unaware that vascular injury has occurred.[1,2]

Nine instances of arteriovenous fistula formation due to great-vessel injury during intervertebral-disk surgery have been reported in the English literature.[1-7] Five of these [1,2,4-6] were recognized only after the development of high-output circulatory failure had caused the patient to seek medical advice months after the operation.

The case reported by Fortune [7] was not recognized during life. His patient died

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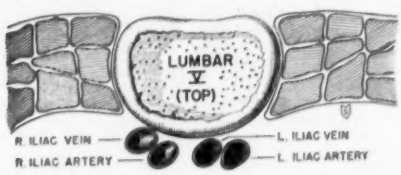
Fig. 1.—Cross sectional drawing at level of L4 to L5 vertebral interspace viewed from above. Proximity of iliac vessels to anterior surface of the vertebral bodies renders them susceptible to injury caused by very slight misplacement of instruments during disk operation.



as a result of a diagnostic misadventure from a hemopericardium and cardiac tamponade, which resulted from a paracentesis of the pericardium. In this instance, a dilated heart from cardiac failure was thought to represent a pericardial effusion, probably tuberculous in etiology. The arteriovenous fistula of the left common iliac artery and vein was a surprise finding at autopsy, three months after the intervertebral-disk surgery.

Significant arteriovenous fistula may escape detection for many years. In one reported instance [8] an arteriovenous fistula of the renal vessels, induced during nephrectomy, was discovered 29 years later, after the patient had been treated for circulatory failure for 15 years.

Data obtained from a questionnaire sent to 100 neurosurgeons [2] suggest that arteriovenous fistula complicates intervertebral-disk surgery more frequently than the number of reported cases would appear to indicate.

It would seem appropriate to include vascular injury incident to intervertebral-disk surgery among the causes of high-output circulatory failure.

Technical advances in the field of vascular surgery, particularly artery and vein repair and graft replacement of damaged blood vessels, provide specific therapy of the high-output circulatory failure resulting from arteriovenous fistula. This should provide further stimulus for the prompt recognition of arteriovenous fistula as a cause for such circulatory failure.

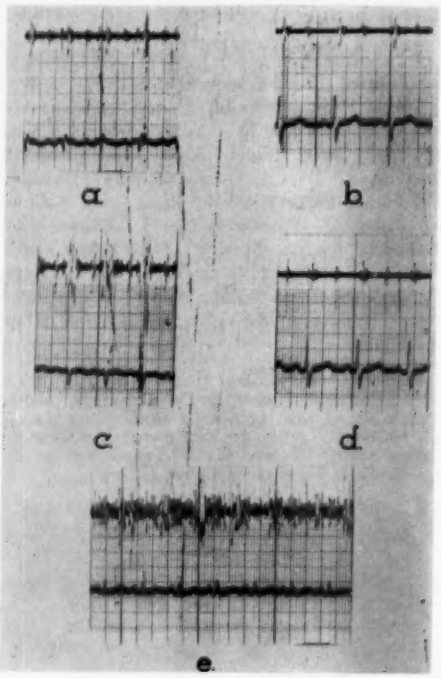
The following examples, seen recently, illustrate the problem.

Report of Cases

CASE 1.—A 36-year-old Caucasian man, active and athletic, with a normal cardiovascular system, was admitted to Walter Reed Army Hospital in September, 1954, for L4 to L5 intervertebral-disk operation. The operation proceeded without untoward incident except for a brief period of increased bleeding, which was controlled promptly by lowering the kidney elevator. Blood pressure of 170/60 and persistent tachycardia of 110 to 120 per minute were recorded. Moderate back pain and nausea continued for 72 hours. He was permitted to dangle his legs over the bedside on the sixth postoperative day. With early ambulation on the ninth day he complained of marked dyspnea and weakness upon mild exertion. Efforts to improve his exercise tolerance by further exercise aggravated the dyspnea. Two weeks after the disk operation he was recognized to be in acute congestive failure.

Physical Findings.—Blood pressure was 200/70 in the upper extremities, and pulse rate was 130 per minute, in marked contrast to preoperative values of 126/76 and 72 per minute. There were moist rales in both lung bases, cardiac enlargement, neck-vein distention, systolic precordial murmur, and gallop rhythm. Arterial pulsations of the right lower extremity were diminished. A pronounced thrill was palpated over the right lower quadrant of the abdomen and over the right femoral vessels. A machinery murmur with systolic accentuation was audible over the abdomen, loudest in the right

Fig. 2 (Case 1).—Phonocardiograms recorded while the patient was in congestive failure with the arteriovenous fistula and again after surgical correction of the fistula. In (*a*), recorded over the pulmonic area, there is a presystolic gallop, no longer present at (*b*), recorded at the same site after repair. In (*c*), recorded over the cardiac apex, there is a presystolic gallop, absent in (*d*), recorded after repair. Tracing (*e*) was recorded over the right lower quadrant of the abdomen and shows the noisy machinery murmur of the arteriovenous fistula.



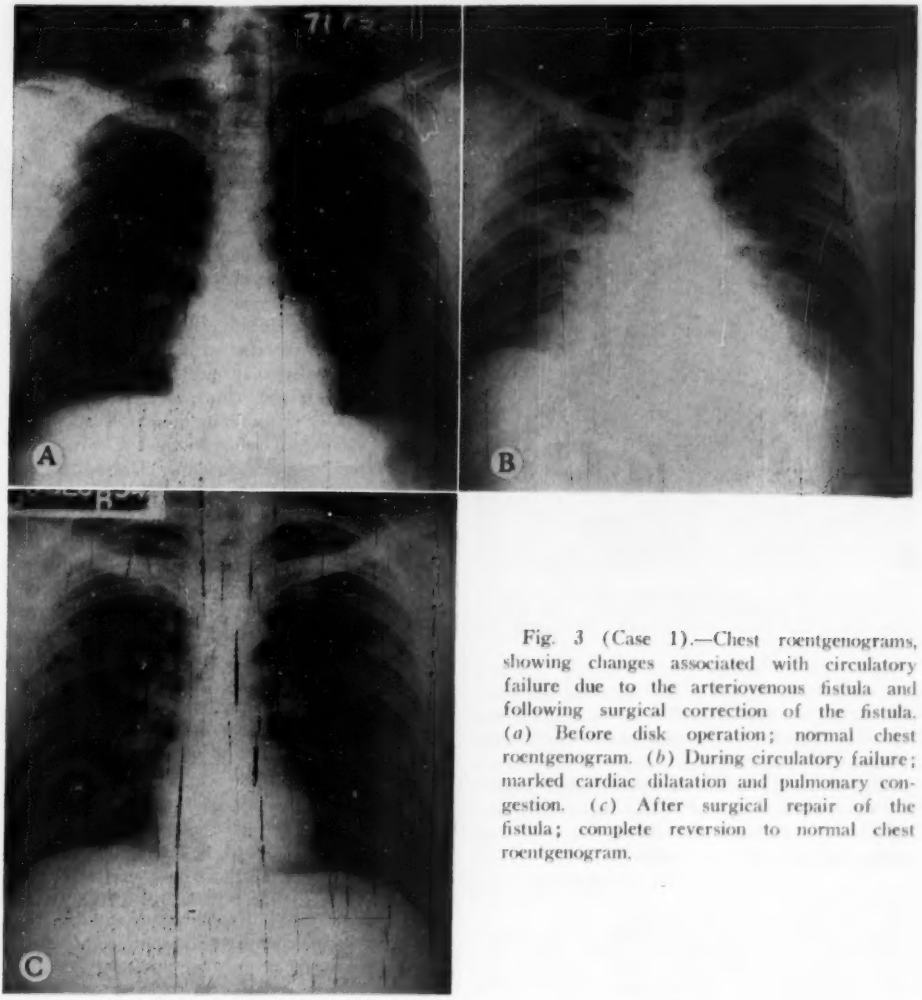


Fig. 3 (Case 1).—Chest roentgenograms, showing changes associated with circulatory failure due to the arteriovenous fistula and following surgical correction of the fistula. (*a*) Before disk operation; normal chest roentgenogram. (*b*) During circulatory failure; marked cardiac dilatation and pulmonary congestion. (*c*) After surgical repair of the fistula; complete reversion to normal chest roentgenogram.

lower quadrant, and radiated up the vertebral column to the cervical region and down the right thigh.

Laboratory and X-Ray Findings.—Urinalysis, hemogram, serologic test for syphilis, and posteroanterior chest roentgenogram (Fig. 3*A*) were normal before the disk operation.

Special Studies.—Phonocardiograms, recorded while the patient was in congestive failure with the arteriovenous fistula and again after surgical repair of the fistula, are reproduced (Fig. 2). In (*a*), recorded over the pulmonic area, there is a presystolic gallop, no longer present in (*b*), recorded at the same site after fistula repair. In (*c*), recorded over the cardiac apex, one again sees a presystolic gallop, absent in (*d*), recorded after correction. Tracing (*e*) was recorded over the right lower quadrant of the abdomen and shows the noisy machinery murmur of arteriovenous fistula.

Electrocardiograms showed a widened precordial transition zone (V_{5-6}) which did not change during the period of observation. Diminished amplitude of T waves improved following surgical correction of the fistula.

Aortogram (Fig. 4) 27 days after the disk operation demonstrated an arteriovenous fistula connecting the right common iliac artery and vein near the aortic bifurcation.

Analysis of the anesthesia record of the intervertebral-disk operation, together with later readings of pulse and blood pressure (Fig. 5), revealed

Fig. 4 (Case 1).—Aortogram, showing arteriovenous fistula between right common iliac artery and vein. The vein and inferior vena cava are markedly dilated.

a sudden rise of systolic blood pressure and pulse rate during the operation. The advent of this rise coincided with the brief period of increased bleeding described above. This is considered to represent the time of formation of the arteriovenous fistula.

Oscillometric study of the lower extremities (Table 1) confirmed the clinical impression of diminished pulsations on the right.

Fig. 5 (Case 1).—Arteriovenous fistula—hemodynamics (right common iliac artery and vein). Graph, showing changes of blood pressure and pulse rate subsequent to formation of the arteriovenous fistula. Note the abrupt increase of pulse pressure and pulse rate (arrow). This occurred immediately after control of the brief episode of brisk bleeding and is believed to coincide with formation of the arteriovenous fistula.

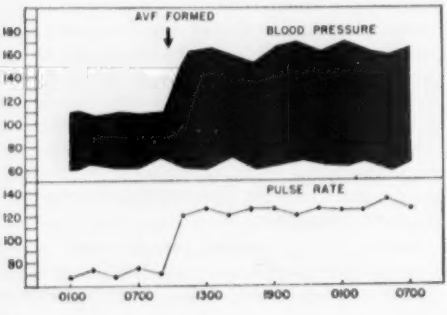


TABLE 1.—*Oscillometric Readings in Case 1**

	Right	Left
Foot	0.00	Faint trace
Ankle	0.75	4.50
Calf	2.50	5.50
Above knee	2.00	5.00

* Collens Oscillometer. Marked decrease of pulsations on the right reflected diminished arterial blood flow through the limb. The fistula shunted blood from the right common iliac artery directly into the iliac vein, bypassing the right lower extremity.

Hospital Course.—Congestive failure increased in severity, manifested by continued tachycardia of 124 to 136 per minute, persistent gallop rhythm, marked orthopnea, and fluid retention. We hoped to delay corrective vascular surgery for four to six weeks in order to permit development of protective fibrosis in the region of the arteriovenous fistula. Venous pressure in the right antecubital vein was 295 ml. of saline solution.

Acidifying doses of ammonium chloride (6.0 gm. per day), followed by injection of mercaptomerin (Thiomerin) (1.0 cc.), repeated after two days, were followed by diuresis and a 7 lb. weight loss. Digitalizing doses of digoxin were administered by mouth. There was partial clearing of pulmonary rales; however, tachycardia, gallop rhythm, and severe orthopnea continued. Chest roentgenogram (Fig. 3*B*) revealed marked cardiac dilatation and pulmonary edema. Because of the severity and refractory nature of the congestive failure we decided to undertake surgical correction of the arteriovenous fistula before the desired four to six weeks had elapsed.

Twenty-eight days after disk surgery the fistula was excised and the involved vessels were repaired. The anesthesia record of this operation (Fig. 6) indicates prompt shift of blood pressure and pulse rate toward normal values when the arteriovenous fistula was excluded from the circulation.

The postrepair course was complicated by several days of ileus and preexisting thrombophlebitis of the left femoral vein. There was a satisfactory response to conservative treatment with rest, elastic wrapping of the lower extremities, and anticoagulant phenindione (Hedulin). All hemodynamic effects of the arteriovenous fistula were reversed following vascular repair. Chest roentgenogram (Fig. 3*C*) demonstrated return of heart size to normal and cleared lung fields. The patient currently manifests no cardiovascular abnormality and is performing the normal duties of a pilot.

CASE 2.—A 44-year-old Caucasian man with a normal cardiovascular system was admitted to an overseas United States Air Force Hospital in January, 1956, for intervertebral-disk surgery. During exploration of the L4 to L5 interspace with pituitary forceps the patient developed abrupt loss of pulse and blood pressure, although less than 60 cc. of blood loss had been noted by the surgeon.

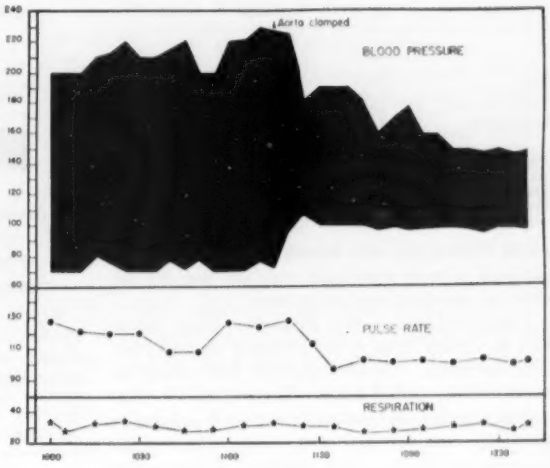


Fig. 6 (Case 1).—Arteriovenous fistula—hemodynamics (right common iliac artery and vein). Graph, showing changes of blood pressure and pulse rate following exclusion of the arteriovenous fistula from the circulation (arrow). Note prompt return of blood pressure and pulse rate to normal values.

Blood pressure and pulse rate returned to previous levels over the succeeding four minutes, during which rapid whole-blood transfusion and high concentration of oxygen were administered. The L5 to S1 interspace was then explored, and the patient was returned to the ward.

Twenty-four hours after the disk operation the patient complained of oppressive precordial discomfort, with a sensation of tightness around the chest and dull abdominal pain associated with mild orthopnea. Blood pressure was 130/40, and pulse rate was 100 per minute, in contrast to preoperation values of 100/60 and 76. No other physical abnormality was noted at that time. Precordial discomfort increased in severity. The possibility of pulmonary infarction was considered. His legs were wrapped, and penicillin and streptomycin were started. Dyspnea and orthopnea increased in severity. The patient became restless and required supplemental oxygen.

Five days after disk surgery there were moist rales in both lungs, cardiac enlargement, liver enlargement, jaundice, arm-to-tongue circulation time (dehydrocholic acid [Decholin]) of 30 seconds, and venous pressure of 295 ml. of saline solution in an antecubital vein. Hematocrit reading had dropped to 31% from a preoperation value of 46%. Chest roentgenogram demonstrated cardiac enlargement and pulmonary congestion. Therapeutic measures included sodium restriction and injections of mercaptomerin.

Seven days after the disk operation a positive search for peripheral vascular abnormality disclosed the findings of an arteriovenous fistula in the left lower quadrant of the abdomen.

The patient was digitalized with lanatoside C (Cedilanid), following which digitalization was maintained by digitoxin, 0.1 mg. per day. A three-day course of mercaptomerin injections was given. Sodium restriction (200 mg. per day) was continued. Moderate clinical improvement accompanied this regimen.

Nine days after disk operation the blood pressure was 160/40 and the pulse rate was 95 per minute. Precordial and abdominal pain decreased in severity. Because of continued fluid retention ammonium chloride and acetazolamide (Diamox) were administered. Marked diuresis followed this therapy. Pronounced lassitude developed and was related to a coincident serum chloride level of 73 mEq. per liter. Jaundice disappeared, the liver decreased in size, and dyspnea improved. The patient was transferred to Walter Reed Army Hospital Feb. 17, 1956, for surgical correction of the arteriovenous fistula.

Physical Examination.—Blood pressure was 150/60 in the upper extremities, 150/70 in the right lower extremity, and 55/no sound in the left lower extremity. Pulse rate was 102 per minute. There was neither pulmonary nor peripheral edema. Neck veins were not distended. Liver and spleen were not palpated. The lower extremities were symmetrical and of normal appearance. The left femoral pulse was diminished in force. Other pulses of the left lower extremity could not be felt. Pulses of the right lower extremity were present and were bounding in character. A continuous thrill was palpated over the left lower quadrant of the abdomen and over the left femoral vessels. A continuous harsh murmur with systolic accentuation was heard over the patient's back, abdomen, and left femoral vessels. The murmur was loudest over the left side of the abdomen and over the left sacroiliac joint. The heart was enlarged to the left. The aortic second sound was split and was much louder than the pulmonic second

TABLE 2.—*Oscillometric Readings in Case 2**

	Right	Left
Foot	0.00	0.00
Ankle	3.50	0.25
Calf	4.50	0.50
Above knee	4.50	0.75

* Collens Oscillometer. Marked decrease of pulsations on the left reflected diminished arterial blood flow through the limb. The fistula shunted blood from the left common iliac artery directly into the iliac vein, bypassing the left lower extremity.

sound. The mitral first sound was accentuated. A Grade 2 systolic precordial murmur was loudest over the pulmonic and aortic areas.

Laboratory and X-Ray Findings.—Upon admission to Walter Reed Army Hospital, 35 days after disk operation, routine urinalysis and hemogram were within normal limits. Posteroanterior chest roentgenogram demonstrated increased pulmonary markings and increased cardiac size. Fluoroscopic examination of the chest disclosed a hyperactive heart, with prominent pulsations of the pulmonary artery and its primary branches.

Special Studies.—Oscillometric study of the lower extremities (Table 2) confirmed the clinical impression that arterial pulsations in the left lower extremity were markedly diminished. Skin temperature studies revealed the left toes to be 1.5 C warmer than the right toes. Review of electrocardiograms taken before and after the disk operation revealed that the transition zone of the unipolar precordial leads had shifted toward the left, from V_{2-3} to V_{3-4} and the appearance of a late R wave in aV_R.

Aortogram (Fig. 7) demonstrated an arteriovenous fistula between the left common iliac artery and vein, with marked dilatation of the vein.

Analysis of the anesthesia record of the intervertebral-disk operation together with later readings of pulse and blood pressure (Fig. 8) revealed a progressive rise of systolic blood pressure and pulse rate beginning during the operation.

Hospital Course.—Thirty-nine days after the intervertebral-disk operation the arteriovenous fistula was excised and the left common iliac artery and vein were repaired. The presence of a large partially organized hematoma, which extended from Poupart's ligament on the left upward to cover the anterior surface of the duodenum, attested to the probability that significant hemorrhage had preceded fistula formation. The massive

Fig. 7 (Case 2).—Aortogram, showing arteriovenous fistula between left common iliac artery and vein. The vein is markedly dilated and bulbous. Vertical density overlying the vertebral column is residual iophendylate (Pantopaque), injected during earlier myelography.

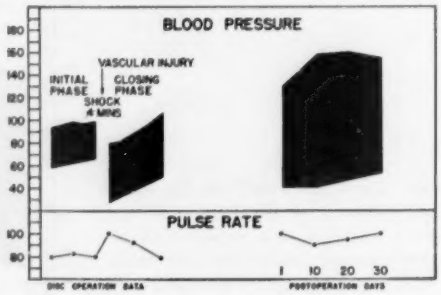
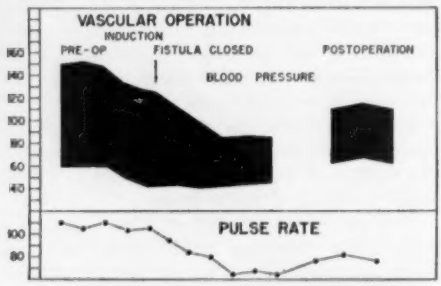


Fig. 8 (Case 2).—Arteriovenous fistula—hemodynamics (left common iliac artery and vein). Graph, showing changes of blood pressure and pulse rate subsequent to formation of the arteriovenous fistula. The episode of shock (arrow) is believed to coincide with the vascular injury. Note widened pulse pressure and tachycardia in the days following the disk operation.

Fig. 9 (Case 2).—Arteriovenous fistula—hemodynamics (left common iliac artery and vein). Graph, showing changes of blood pressure and pulse rate following exclusion of the arteriovenous fistula from the circulation (arrow). Note normal values following surgical correction of the fistula.



hemorrhage undoubtedly had caused the brief episode of shock during the disk operation.

Analysis of the anesthesia record during the vascular repair (Fig. 9), as in Case 1, indicated rapid change of blood pressure and pulse rate toward normal values after the arteriovenous fistula was excluded from the circulation. Pulses of the left lower extremity returned at once.

The patient's subsequent course was characterized by complete restoration of normal circulatory status. Twelve days after corrective vascular surgery blood pressure was 100/60 in the upper extremities and 160/80 in each lower extremity. Pulse rate was 80 per minute. Heart size, peripheral pulses, and exercise tolerance were normal. Digitalis was no longer required. Electrocardiogram indicated return of precordial transition zone to V_{3-5} and absence of the late R wave in aV_R. The patient currently manifests no cardiovascular abnormality and has returned to normal activity as a pilot.

Pathophysiology

Reduced resistance to peripheral runoff of blood from the systemic arterial tree is a major factor in the production of high-output circulatory failure. Arteriovenous fistula of appropriate size in the peripheral circulation affords an escape for blood from the systemic arterial tree into the venous system. Circulatory adjustments to acute formation of a significant arteriovenous fistula manifest as immediate and late effects.[9]

Immediately, sudden massive runoff of arterial blood into the venous bed results in transient decrease of arterial volume and increase of venous volume. General arterial blood pressure falls, both systolic and diastolic. Venous pressure rises. Pulse rate and cardiac output rise as immediate compensatory adjustments to the lowered arterial volume and blood pressure.

Late effects result from continued runoff of arterial blood through the fistula. There is an increase of blood volume roughly related to the size of the fistula. Venous pressure rises, tachycardia continues, cardiac output remains high, cardiac dilatation develops, and there is progressive rise of arterial blood pressure from its immediate low-level response to a systolic pressure equal to or higher than the prefistula level. Diastolic pressure remains low.

The size of the involved vessels, the size of the fistula, and peripheral resistance at the site of the fistula are important because they affect the magnitude of the circulatory response to formation of the fistula.[10]

Whether circulatory failure occurs is ultimately determined by the degree to which increased cardiac output provides the systemic capillary bed with enough blood to compensate for that lost through the fistula. When blood flow through the fistula is very great or when the myocardium weakens so that cardiac output falls significantly systemic capillary flow decreases. Salt and water are retained, probably by mechanisms of decreased glomerular filtration[11] and of diminished renal tubular excretion of sodium chloride.[12] With salt and water accumulation venous pressure rises; the heart dilates excessively; cardiac output drops to an insufficient level, although still elevated above normal values, and circulatory failure ensues. Since the circulatory failure occurs with a cardiac output which exceeds normal levels this entity is termed "high-output circulatory failure." The physiology of arteriovenous fistulas and the factors leading to high output failure were recently well summarized by Schreiner[13] and included many of the clinical and laboratory observations made during study of numerous traumatic arteriovenous fistulas seen at Walter Reed Army Medical Center during and after hostilities in Korea.

It is a curable form of heart disease because elimination of excessive runoff of arterial blood (by correction of the fistula in this case) reduces the demand for cardiac work to normal levels and restores a normal cardiodynamic state.

Comment

Classical features of high-output circulatory failure due to arteriovenous fistula were illustrated by the foregoing cases. Each case resulted from great-vessel injury which was not recognized during intervertebral-

disk operation. In each case circulatory abnormalities reversed dramatically following surgical repair of the fistula. These included increased pulse pressure, tachycardia, cardiac dilatation, arterialization of the involved venous system, diminished arterial pulsations and blood flow distal to the fistula, and high-output circulation failure.

Although signs of vascular injury during intervertebral-disk operation are not prominent, certain events may provide the surgeon or the anesthetist with information leading to recognition of vascular injury, particularly if an arteriovenous fistula is induced. These include an abrupt rise in pulse rate, widened pulse pressure, sudden hemorrhage which is easily controlled, and an episode of shock disproportionate to the amount of observed blood loss.

During the postoperation period persistent tachycardia, untoward dyspnea, cardiac enlargement, and edema of lower extremities are suggestive of fistula formation and should prompt a search for signs of arteriovenous fistula. Physical signs to be looked for are unilateral venous dilatation, venous pulsation, diminished arterial pulsation of a lower extremity, palpable thrill over the lower abdomen and femoral vessels, audible machinery murmur with systolic accentuation over the lower abdomen and femoral vessels, tachycardia, widened pulse pressure, cardiac enlargement, increased venous pressure, and circulatory failure.

Lest an erroneous impression arise regarding neurosurgical technique it should be emphasized that vascular injury during intervertebral-disk operation has occurred at the hands of the most competent surgeons fully aware of the danger. As stated by Holscher,[3] describing his case, ". . . . The ease with which this complication can occur can only be appreciated by the surgeon in whose hands such an unfortunate incident has happened."

It has been stated that restoration of the vascular channel is not always essential; occasionally ligation may be simpler and safer.[6] While it is recognized that the surgeon can safely ligate the common iliac artery in some instances, after collaterals have developed around the arteriovenous fistula, there is always the danger of subsequent arterial insufficiency, even if gangrene does not occur. A viable extremity is not always a good functional extremity. Also, patients who are severely decompensated may not tolerate the delay required for the development of collateral circulation.

Since this is a form of heart disease which may be cured by operation, it is reasonable that the operation to alleviate the heart condition should also restore continuity of the injured vessels. The two cases reported here are two more instances in which the fistula was excised and both the artery and the vein were reconstructed.

The important features of specific curability, inapparent relationship to previous operation, and a probable incidence greater than the number of reported instances would indicate emphasize the desirability of inviting attention to this problem of high-output circulatory failure complicating great-vessel injury during intervertebral disk operation.

Summary

High output circulatory failure is an unusual complication of intervertebral-disk operation. Inadvertent injury to close-lying great vessels during the operation may result in the formation of an arteriovenous fistula. Circulatory adjustments to the fistula with eventual development of circulatory failure may cause the patient to seek medical treatment months or years after the disk operation, at a time when the causal relationship to a previous operation may not be apparent.

Two examples of this complication, involving common iliac arteries and veins, are described. In each instance the patient was sent from the operating room by a surgeon and an anesthetist both unaware that significant vascular injury had occurred. The complication was recognized only after the development of high-output circulatory fail-

ure in each case. Classical signs of large arteriovenous fistula were present.

Surgical correction of the fistula with restoration of normal blood flow through the involved vessels resulted in prompt and complete reestablishment of normal circulatory dynamics.

Awareness of the possibility that circulatory failure may be related to previous disk operation and careful examination for evidence of arteriovenous fistula may shorten the time lag between vascular injury and specific diagnosis and treatment.

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Treatment in Internal Medicine

Practical Aspects of Long-Term A nticoagulant Therapy

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The clinician is more and more frequently confronted with the decision as to whether or not to give a patient anticoagulants beyond his hospital stay. Indications for long-term therapy are quite definite in some conditions and less so in others. Once the decision is made to continue such therapy over a period of months or years the burden on both patient and physician may be materially eased if certain principles are understood and practices followed. Since long-term therapy with heparin is for the most part impractical, it is the prothrombin depressants with which the clinician is chiefly concerned in prolonged anticoagulant administration. It is the purpose of this paper to discuss briefly certain principles of such therapy and to emphasize the practical aspects of their application.

Methods of Control

Despite recent advances in our knowledge of the mechanism by which blood clots, our assays for clotting factors are still not specific. The safe and effective administration of the prothrombin depressants is dependent upon a reliable method of control. This, unfortunately, is not generally available at the present time. Until recently the so-called prothrombin-depressant drugs were considered to affect primarily prothrombin and to have little influence on other clotting factors. There is a growing body of evidence, however, to indicate that factors other than prothrombin, particularly the accelerators, Factor VII,[1] and, to a smaller degree, Factor V,[2,3] are also reduced. Furthermore, plasma thromboplastin component (Factor IX, Christmas factor), a plasma constituent essential to the formation of thromboplastin in blood, has been reported by a number of workers to be depressed by a variety of anticoagulants.[4-8] It appears that the reduction of various coagulation factors as a result of therapy varies from drug to drug[9] and patient to patient,[10,11] and it is quite possible that additional known or still unknown factors may also be affected.

The administration of these drugs is controlled almost universally by means of the one-stage prothrombin assay (the prothrombin time).[12] While this was considered originally by Quick to be a specific measure for prothrombin, subsequent experience has shown that the prothrombin time is also a function of other variables.[13,14] A further complicating feature of the test is the recent discovery that the various thromboplastin preparations used in the assay, all of which are of animal or human tissue origin, contain varying amounts of Factors V and VII.[15,16] Thus, we may be adding to the test system some of the very factors which we are assaying. These differences in the thromboplastins themselves are, we believe, at least in part responsible for the varying prothrombin results obtained from time to time and hence the resulting occurrence of unexpected hemorrhages in some cases and the apparent failure of anticoagulant therapy in others. Such often unpredictable clinical effects are largely responsible for the wide difference of opinion as to the safety and efficacy of these drugs. Despite these diffi-

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culties many patients are being given anticoagulants with apparent safety and benefit. Thus, when administered carefully the advantages of therapy far outweigh its possible disadvantages. In this connection the availability of the two-stage prothrombin assay [17] and the TAMe method [18] adds appreciably to the ease of control of this form of therapy.[19,20] While these procedures are also influenced by the additions of Factors V and VII in the thromboplastins, they both separate the two stages of the clotting mechanism, and practical experience has shown that they produce considerably less variable prothrombin results than the one-stage technique. We have used a combination of the one-stage and two-stage tests for over a decade with gratifying results. Whatever method or methods are used, their constant close surveillance is essential to safe and efficient therapy. The commonly used one-stage test involves the addition of tissue juice (thromboplastin) to oxalated or citrated plasma, subsequent recalcification, and measuring the time of the appearance of fibrin. Some laboratories report their results in seconds, others prefer to convert the observed time to "percentage prothrombin." In our opinion the latter manner of reporting is preferable, since (*a*) it places the burden of accuracy on the laboratory, (*b*) it provides for less variation in interpretation, and (*c*) it provides for easier control when the patient moves from one geographical area to another and blood samples are processed by different laboratories.

When the results are expressed in terms of percentage prothrombin it is advisable to run a "normal curve" once a week and more often if the batch or type of thromboplastin is changed. It may also be important to select the thromboplastin providing the greatest variation in the prothrombin times of normal and therapy plasmas, since, as previously explained, the latter may be deficient in their content of various accelerators. The particular preparation selected in this manner will be the one exhibiting, at least comparatively, the lowest accelerator activity. Such a preparation will be more likely to provide a true picture of the over-all thrombin-forming capacity of a given therapy plasma.

Choice of Drug

There are commercially available at the present time eight prothrombin-depressant drugs. Of these, six are coumarin derivatives: bishydroxycoumarin (Dicumarol), cyclocumarol, ethyl biscoumacetate (Tromexan Ethyl Acetate), warfarin, Marcumar (3-[1-phenylpropyl]-4-hydroxycoumarin), and acenocoumarin (Sintrom). The other two are indandiones: phenindione and diphenadione (Dipaxin). The in vivo actions of the two groups of drugs appear to be grossly similar in nature in that they depress prothrombin and Factor VII, Factor IX, and to some degree Factor V. However, there do seem to be differences between the various drugs in (*a*) the rate at which they reduce the plasma concentrations of individual clotting factors,[11] (*b*) the actual levels to which the factors are reduced, and (*c*) the rate at which the factors return to normal following the withdrawal of the drug. From the point of view of their over-all induction and recovery periods the eight drugs may be grouped into three categories: (1) bishydroxycoumarin and cyclocumarol, having slow induction and slow recovery periods; (2) ethyl biscoumacetate, phenindione, and acenocouramin, having rapid induction and rapid recovery periods, and (3) diphenadione, Marcumar, and warfarin, providing rapid induction and slow recovery.

There are no particular advantages to bishydroxycoumarin and cyclocumarol except those of known reliability and familiarity. They are safe and efficient and as satisfactory as any of the others for long-term therapy. The drugs with shorter induction and recovery periods provide for earlier control and hence allow the parallel use of heparin to be discontinued earlier. They also provide for more rapid decontrol in case of hemorrhage, trauma, or required

surgery. The patient and physician using them must be aware of the importance of regular dosage, since the omission of one day's dose may result in "escape" from the therapeutic bracket. In the case of phenindione it is wise to use the divided daily dose in order to prevent such escape.

Those drugs with short induction periods and prolonged recovery times, diphenadione, Marcumar, and warfarin, have the advantage of a lesser tendency to produce variations from the therapeutic bracket (10% to 30% of normal prothrombin), and the omission of one or two doses can readily be compensated for before the prothrombin "escapes" from this bracket. This property of a long recovery period is a disadvantage in case rapid return to higher prothrombin levels is desired in the event of serious bleeding or the necessity of early surgery. This disadvantage, however, may be almost completely overcome by the administration of vitamin K-active substances.

If short-term therapy is anticipated one of the drugs from Group 2 may be selected to advantage. They also may be chosen in cases which may require surgery within a short time after therapy is instituted.

For long-term therapy, on the other hand, the clinician will find the long-acting anticoagulants of Group 3 quite satisfactory.

Factors Influencing Uniformity of Control

In addition to the factors discussed earlier, under "Methods of Control," there are a number of others which may influence prothrombin levels. Among these are poor liver function, general nutritional state, diet, other drugs, alcohol, patient cooperation, individual tolerance, and, lastly, the experience of the clinician with the particular anticoagulant.

Poor liver function, and/or nutritional deficiency usually render the patient more tolerant of the effects of a prothrombin depressant and less responsive to vitamin K administration. A diet poor in proteins appears to be associated with frequent variation in prothrombin levels. On the other hand, a diet rich in leafy green vegetables, and particularly a supplemental capsule containing vitamin K, will often increase the tolerance to an anticoagulant.

The methylxanthines, caffeine, and, more recently, some of the tranquilizing drugs may increase the tolerance to prothrombin depressants. Contrariwise, the salicylates (which break down to coumarin substances) may precipitate a drop in prothrombin levels. Patients should be cautioned against the taking of more than 15 grains (0.97 gm.) of salicylate a day without first consulting their physician. Several of our patients have developed severe hypoprothrombinemia and hematuria as a result of excessive salicylate intake during upper respiratory infections. Alcohol elevates prothrombin levels, and patients who use alcoholic beverages must be advised to take the same amount daily in order that their anticoagulant intake may be adjusted to it.

It goes without saying that complete patient cooperation is essential to properly controlled anticoagulant therapy, and the greater the experience of the clinician with the various drugs the more uniform will be the control. In general the drug with which the clinician is most familiar is the one he should use.

Some patients appear to have idiosyncrasies to certain drugs, and when, despite a careful check of the above factors, a patient's prothrombin continues to vary a shift to another anticoagulant will often remedy the difficulty.

Frequency of Prothrombin Determinations

The length of the interval between prothrombin tests will depend upon the stage of therapy, the stability of the individual patient's prothrombin level, and, to some extent, the particular drug in use.

In the early stages of therapy daily determinations are usually indicated. After the prothrombin level has become reasonably stabilized within the therapeutic bracket the

interval may be extended to two days, then to three days, four days, and eventually to two weeks. This latter interval is usually not attained in less than two months after the initiation of therapy, since the stability of any patient's prothrombin level can rarely be trusted earlier.

A prothrombin level of less than 10% will, of course, call for frequent tests, although the stage of therapy, the drug, and previous knowledge of the patient's behavior while taking the drug will influence the required frequencey of the tests. If a patient has been given therapy for some months and his prothrombin has been well stabilized a level of 5% should not be alarming. It is well to inquire into a possible change of routine on the part of the patient (Factors Influencing Uniformity of Control). Often, however, there will be no discoverable cause for the depressed prothrombin value. If a long-acting drug is being used a single daily dose may be omitted and a test made in one week. If a short-acting drug is involved the dose should be reduced, not omitted, and a test made the following day, since a rapid rise may be expected, and an "escape" to above therapeutic levels must be averted. Such a "titration" from below therapeutic to therapeutic levels may usually be accomplished without great difficult. The patient is advised to observe a urine specimen twice daily during the period of a depressed prothrombin and to report any signs of bleeding. As a rule a prothrombin level must be below 10% for several days before hematuria develops. Weekly or semiweekly tests may be necessary until the prothrombin is again stabilized.

The interval between tests is never extended beyond two weeks. We have observed patients given the same dosage of a drug for months with less than 10% variation in the prothrombin level who without apparent reason jump to 80% or drop to less than 1%. If such a change is allowed to compound itself for too many days serious bleeding or even more serious clotting may occur. We have rarely seen this happen when prothrombin determinations are made at a maximum interval of two weeks.

Countermeasures

It may be necessary at times to neutralize rapidly the effects of anticoagulant drugs. This may be as a result of hemorrhage, trauma, or required surgery.

If the hemorrhage is not severe, i. e., is limited to hematuria, gross or microscopic, and/or mild bruising, and if the prothrombin is above 5% by the one-stage method, withdrawal of the drug may be all that is necessary. This is particularly true if the drug is one characterized by a short recovery period. The patient is instructed to collect single urine specimens and line them up along the window shelf. He reports their appearance every 12 hours, and if consecutive specimens are deepening in color another prothrombin determination is carried out. If it indicates a lower level than the previous one, a small amount (10 mg.) of vitamin K may be given by mouth or vein and the urine observed during the subsequent 12 hours. This will usually prove effective, though of course more vitamin K is indicated if it does not. As a rule vitamin K will not be necessary, and the urine will begin to show less blood shortly after the anticoagulant is withdrawn. This is particularly true if one of the drugs of Group 2 is being given. Therapy should be resumed cautiously when the urine is completely free of blood.

We prefer to use water-soluble vitamin K-active substances rather than phytonadione (vitamin K_1) or K phytonadione oxide, since the latter tend to render the patient refractile to further anticoagulant administration. The effects of all prothrombin depressants except diphenadione can be effectively neutralized with the use of water-soluble vitamin K substances. Even so it is proper to use small doses, 5 to 20 mg., of phytonadione when one is trying to counteract the effects of diphenadione.

It is not necessary to use vitamin K when the patient's prothrombin is below 10% of normal and no bleeding is present. This is true even with the longer-acting drugs. Withdrawal of the drug and careful observation of the prothrombin level is the more desirable course. If the prothrombin becomes further depressed careful titration of it to the therapeutic bracket should be done. This can be achieved with phytonadione in the presence of diphenadione effect, and the development of a refractivity to the drug thus be avoided.

The parallel use of both the one-stage and the two-stage assay methods is of especial advantage in the instance of prothrombin levels below the therapeutic bracket. The results of the one-stage usually run 5% to 15% higher than those of the two-stage, and bleeding rarely occurs until both tests register levels below 10%. Since the one-stage is subject to more sudden and greater variations than the two-stage, there is less warning of impending dangerous levels when it alone is used for the control of anticoagulant administration.

Decontrol

The decontrol of anticoagulant therapy ordinarily presents no problem. Since thrombosis has occurred in some instances when the drugs have been suddenly withdrawn it is usually safer to discontinue them gradually. This provides for a slow return to normal prothrombin levels, and the latter may be checked at monthly intervals for a two-month period.

Of particular importance is the technique of decontrol of a patient with atrial fibrillation and a history of embolism. Such patients may require surgery, and unless it is of an emergency nature the decontrol should be gradual and completely covered by supplemental intravenous heparin administration. The prothrombin depressant can be withdrawn and heparin given at four-hour intervals while the decontrol is in progress. Once daily the interval is extended to six hours and a prothrombin assay made at the end of that time. This is necessary because heparin interferes with the prothrombin assay, and the heparin effect must be eliminated before the blood sample for the prothrombin determination is drawn. Surgery can be carried out when the prothrombin has reached 75% or more, but the heparin is continued until four hours prior to surgery. It is restarted along with the prothrombin depressant six hours after surgery and continued until the prothrombin is again within the therapeutic limits. We have seen fatal emboli when such a routine has not been followed.

Summary

The administration of anticoagulant drugs over an extended period of time is a safe and effective form of therapy when properly controlled. The practical aspects of such therapy have been discussed briefly and include methods of control, choice of drug, frequency of prothrombin determinations, factors influencing uniformity of control, countermeasures, and decontrol.

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Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. Archives of Internal Medicine, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

A Brief History of the Portal Circulation

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A perusal of the early history of the human race would suggest that the liver might easily have been the first of the internal organs known to man. Hepatoscopy, the reading of omens in the signs noted on the liver of sacrificial animals, was one of the oldest and widespread methods of divining the future, both among the primitive peoples and among the several civilizations of antiquity. Among the Babylonians, soothsaying was concentrated upon the liver. Terra cotta models of these livers estimated to be about 3000 years old have been found, the surfaces of which have been divided into squares and studded with prophetic inscriptions. Similar models of the liver have been found at ancient Hittite sites in Asia Minor, and Etruscan livers in bronze, dating from the third century B. C., have been found near Piacenza. The drawings of these models pictured by Stieda [1] show the general gross contour and lobulation of the liver, as well as the gallbladder and external ductal system of the liver, but there is no suggestion of the vessels of the liver.

In view of the ancient familiarity with the liver and the fact that hepatoscopy represented the starting point for the study of animal anatomy in general, it seems rather surprising that no adequate description of the portal vessels existed, even to the time of Galen.[2,3] The porta hepatis apparently derived its name from the anatomical formation in the sheep, where there is a deep depression separating the two lower lobes from the caudate lobe, giving the appearance of a gate with columns on either side. The large vein entering the gate thus became the vein of the gate, or portal vein.

Galen believed that the blood was perfected and had its central source in the liver, to which the portal vein brought a cruder liquid derived from the products of digestion. He believed that the blood left its source in the liver by way of the roots of the venous system, the modern hepatic veins. From the liver, Galen believed that the blood then divided into two streams, one going upward and one downward.

As anatomic dissection became more widespread, the opinion of Galen that the liver was the site of origin of the blood began to be doubted. Vesalius pointed out that the grossly lobulated form of the liver was peculiar to animals and not present in his dissections on man. It is interesting that Leonardo da Vinci,[2] who made beautiful anatomical sketches of the circulatory system, showed the liver as a sort of appendage to the caval system just above the renal veins. Fabricius [3] (1603) was aware of the manner of union of the hepatic veins with

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the vena cava, but his illustrations do not include the portal system.

The first modern understanding of the circulation of the liver dates from 1628, when Harvey [4] published "An Anatomic Dissertation Upon the Movements of the Heart and Blood Vessels in Animals." To quote a passage in this regard, he stated, "It may be that those of the mesentery imbibe the chyle from the intestines and carry it mixed with the blood to the liver, for the blood entering the mesentery by the coeliac artery and the superior and inferior mesenteries proceeds to the intestines, from which, along with the chyle that has been attracted into the veins, it returns by their numerous ramifications into the vena portal of the liver and from this into the vena cava and thus in such wise that the blood in these veins has the same color and consistency as in other veins." He believed that nature interposed the liver to rid the blood of the small amount of chyle. Harvey also was aware that the embryo did not utilize its liver, so that the umbilical vein bases directly to the heart.

Perhaps the most comprehensive study of the human liver at this time was that of Francis Glisson,[6] who in 1654 published his "Anatomia Hepatis." Glisson studied and illustrated the intrahepatic relationship of the portal and hepatic vasculature. According to Gans,[7] it was Kiernan who introduced the erroneous name "capsule of Glisson" in reference to the portal canals rather than to the hepatic capsule, which really had been described in 1640 by Waleus. Glisson also clearly demonstrated that the portal blood passed through the liver into the vena cava. He filled a large ox bladder with water and milk and connected it to the portal vein. On squeezing the bladder, milky water passed through the liver, entered the vena cava, and then entered the right side of the heart. He noted that the liver slowly lost its red color and became pale, an observation which led him to suspect that the portal blood bathed the capillaries as well as the large vessels. He speculated also upon the question as to why, with so rich a venous supply, the liver needed such a rich arterial supply.

When in 1669 Malpighi [5] published his observations demonstrating the capillaries and expressing the opinion that the liver was a "conglomerated or clustered glandule," the Galenical opinion finally was laid to rest.

There appeared to be a pause in the acquisition of further knowledge of the circulation of the liver for a considerable period of time. In 1748, Lieberkuhn [9] introduced the injection techniques for anatomic studies and noted that in the liver all the vessels appeared to connect with each other.

In 1833, Francis Kiernan [10] published a complete description of the hepatic vessels. Among other observations he noted the presence of a block, so that when the hepatic vessels were injected no blood appeared in the portal vein or in the hepatic artery.

The gross anatomic knowledge up to this time is summarized in some beautiful anatomic drawings published by Jones Quain,[11] in 1836.

Physiologic and pathologic observations in relation to the liver began to appear in the literature after the clarification of the anatomic picture. Stahl,[12] in 1748, apparently realized that there was connection between the portal, splenic, and hemorrhoidal veins. In 1757 William Hunter had noted pulsation of the liver in a patient with a large arteriovenous fistula after venous section and that the pulsation had disappeared after closure of the fistula. Cruveilhier's [13] description of venous collateral after disease of the portal vein appeared in 1834. He was aware of the fact that the blood could flow in either direction in these large abdominal wall collaterals. Braune,[14] in 1884, published nine cases with typical caput medusae.

The first description of a patient with cirrhosis who bled to death from a varix was by an American, W. Power, in 1840.[15] He reported the case of a 50-year-old Negro man who bled to death after a period of

hepatic insufficiency and at autopsy was found to have varicose veins of the esophagus with an ulcer over one cluster. Power noted that at that time he could find no similar case reported. A similar isolated case was reported by Fauvel in 1858. Frerichs,[16] whose textbook on diseases of the liver was published in 1858, believed Fauvel's case to be a rare occurrence.

An extremely interesting paper was published by Preble,[17] in 1900. He reported 4 cases of his own and collected 56 cases from the literature where death had been due to bleeding varices. Preble was aware of the fact that not all cirrhotics who bled had varices as the source of hemorrhage and that not all patients who bled from varices had cirrhosis. He also noted the presence of gastric varices and the fact that the development of the collateral circulation altered the course of the disease. He apparently measured the pressure in the veins, as he reports it as 14-18 mm. of Hg, a measurement now known to be low. He further stated that the French had designed an intraesophageal bag which could be filled with water and used to control the hemorrhage.

Meanwhile, many clinicians were reporting the curious fact that the liver apparently could function normally even though at autopsy there appeared to be extensive destruction of liver substance. Malcolmson,[18] in 1839, reported a series of patients with huge liver abscesses, none of whom were jaundiced. Claude Bernard,[19] in 1877, demonstrated experimentally that the hepatic veins contained less sugar than the portal vein. Cohnheim,[20] in 1876, in a detailed pathological report on the liver of a patient who had died of obstruction to the portal vein noted the dilation of the hepatic arterial circulation and speculated upon the reciprocal relationship of the hepatic artery supply to the portal venous supply.

A real stimulus to the study of the portal circulation was the report by N. V. Eck,[21] in 1877, on the establishment of a fistula between the portal vein and the vena cava. Although his work was directed primarily toward the idea that ascites could be relieved in this manner and although his longest-surviving animal lived only three months, Eck's conclusions have stood the test of time. He published his paper in an obscure Russian journal, *Voyenno-meditsinskii Journal*. Eck's work was brought to the attention of European investigators by a very long and thorough study of this problem by Hahn, Messen, Nencki, and Pavlov,[22] in 1893. It is of interest that an autopsy on a patient with a spontaneous Eck fistula had been reported by Abernethy in 1793.[42]

In 1907 Herrick,[24] in a perfusion study of livers, noted the large amount of blood under low pressure in the portal vein as opposed to the small amount of blood under high pressure delivered by the hepatic artery. In 1928 McIndoe[25] suggested that in cirrhosis the portal pressure must be elevated, an opinion that was supported by McMichael[26] from his studies on congestive splenomegaly. Actual measurements at operation of these elevated pressures were reported by Rousselot[27] in 1939, who noted pressures as high as 400 mm. of saline in the portal bed.

While other observers had commented upon the fact that the hepatic artery exerted an effect on the portal venous pressure, Dock, in 1942,[28] was the first to suggest ligation of the hepatic artery as a means of lowering the portal pressure. Surgical trial of this method was attempted by Rienhoff, in 1951. A summary of the problems of hepatic artery ligation has been published by Ranström.[29]

Apparently the first successful Eck fistula was constructed in man by Vidal,[30] in 1903. In this country the operation was revised by Whipple, in 1943, and large clinical experiences with the method have been reported by Blakemore, Linton, Welch, Child,[31] and many others.

Accurate measurements of liver flow and changes in portal pressure have been reported by wedging catheters into the hepatic veins. Meyers and Taylor[32] first studied

this method in 1951 on the basis of the work of Dexter, who measured reflections of pulmonary venous pressure by wedging catheters into the pulmonary artery. Meyers and Taylor tried the method out on the livers of cats. They then reported observations on 12 patients without liver disease and on 7 patients with cirrhosis. Their work was confirmed and extended by Paton, Reynolds, and Sherlock,[33] in 1953.

The introduction of opaque media into the portal circulation by splenic puncture was developed by Daniel and Prichard,[41] in 1951. By the use of this method not only can the site of portal obstruction be determined accurately but considerable information has been accumulated on retroperitoneal collateral channels and presence of clots in the major veins.

Some mention should be made of the part played by the liver in shock. It was pointed out by Fine[34] that the irreversibility of hemorrhagic shock in the dog could be prevented by perfusing the portal circulation. This observation was confirmed by other observers,[35] who created portal hypertension by arterializing the portal vein by means of a graft between the aorta and the proximal end of the portal vein. Many interesting physiological observations have been made by the use of this method. It has been tried clinically in Japan by Kimoto[36] and in Italy by Pettinari,[37] in 1952, as a method of therapy in portal cirrhosis. The latter author reported four cases, two of which allegedly were improved by the method. Hunt[43] also attempted renal artery to portal vein anastomosis in four cases, without success. Himsworth[38] suggested in 1947 that the teleological explanation for the double circulation of the liver was the protection effect of the arterial oxygen delivered to an essential organ during an alarm reaction when the venous pressure might be zero. The arterialization experiments would tend to bear out the protective function of the hepatic arterial supply for the liver.

The microscopic vascular arrangements of the liver have been intensively studied by Elias[39] and Knisely.[40] Many bypassing and sphincteric mechanisms have been postulated, but the clinical and pathological importance of these mechanisms is uncertain.

Similarly, the relationship of the rich lymphatic and nerve supply of the liver to its blood supply is indefinite.

No attempt has been made in this brief review to look into the pharmacological investigations upon the circulation of the liver. Suffice it to say that there appears to be a marked species difference in behavior, especially concerning the sphincteric action of the hepatic veins.

For a definitive bibliography on the circulation of the liver, the reader is referred to the excellent monograph of Child,[31] from which I have freely drawn.

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Books

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BOOK REVIEWS

Allergie. Third edition. By H. E. Bock et al. (24 contributors). Edited by Prof. Dr. K. Hansen. Price, DM 187; $44.50. Pp. 1212, with 305 illustrations (some in color). Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N; Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16, 1956.

The third edition of this standard text is an impressive accomplishment. The contributors—Europeans, but mostly Germans—are well-known authorities in their respective fields. My former teacher, the late Professor Rössle, wrote the chapters on the investigative history of allergy and on the clinical pathology of allergic diseases; Klinge and Fassbender, the chapter on the experimental pathology of allergy. The editor, Professor Hansen, contributed chapters on functional changes which are the result of antigen-antibody reactions; on sensitizing agents; on diagnostic procedures, and the chapters on clinical allergies of the respiratory tract, the gastrointestinal tract, and the nervous system. No aspect of allergy is omitted; the book has been put together with a craftsman's attention to detail. The fact that it ends with a comprehensive review of allergic diseases in animals (Wagener) might convey a rough idea about its design.

It is, perhaps, understandable that such an ambitious project cannot be without flaws. The chapters are uneven; some are clear and precise, some (such as the section on the etiology of bronchial asthma), confused by the obvious attempt to be all-inclusive rather than critical. The book contains its share of dogmatic pronouncements which, as the list of allergens which are capable of producing kidney damage, are not supported by acceptable evidence. In fact, one finishes the book with a feeling that it has stretched the meaning of "allergy" to the widest permissible limit.

The textbook makes it apparent that science and scientists are still hesitant to cross national borders; large blocks of investigative work published here during the past decade are missing in this encyclopedia. Several of the bibliographies are sketchy, and many of the contributors have the annoying habit of citing names in the text but not in their references.

Even with its shortcomings, the literature on allergy does not, to my knowledge, offer any "Handbuch" which can compare in scope and execution with this astonishing effort.

MAX SAMTER, M.D.

Lupus Nephritis. By Robert C. Muehrcke, M.S., M.D.; Robert M. Kark, F.R.C.P., F.A.C.P.; Conrad L. Pirani, M.D., and Victor E. Pollack, M.D., M.R.C.P.E. Price, $3. Pp. 145, with 53 illustrations (10 color). Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1957.

This monograph is a discussion of one aspect of disseminated lupus erythematosus and originally appeared in the March, 1957, issue of *Medicine*. The authors attempt to describe in detail the pathological features of lupus as it affects the kidney, to characterize its method of progression in that organ, and to correlate the structural changes in the kidney with ordinary clinical laboratory measurements of renal function. The study represents one of the first major contributions to clinical medicine made by using the technique of renal biopsy.

I was struck by the careful attention to detail in the descriptions of the renal biopsies and the care with which the pathological picture was developed. There are very good pictures of the pathologic lesions and a number of color plates of the same material which add greatly to the descriptions in the text. The correlation of the pathologic material with clinical renal function studies is weakened to a certain extent by the nonspecificity and crudeness of the clinical studies. The conclusions that no single test was superior to a combination of the

* Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmissal to him.

concentration, urea clearance, and PSP tests and that all three tests gave an excellent over-all impression of underlying damage parallel observations made with these tests in other diseases involving the kidneys.

The final section of the book, which has a discussion of the relation of lupus nephritis to other diseases affecting the blood vessels of the kidney, is a useful differential diagnostic exercise and points out succinctly the value of the kidney biopsy.

This monograph is one which can be read with profit by all who are interested in medicine and kidney disease. It will serve as a storehouse of information concerning lupus erythematosus and the value of the renal biopsy. I recommend it without qualification.

WALTER M. KIRKENDALL, M.D.

Archiv und Atlas der normalen und pathologischen Anatomie in typischen Röntgenbildern: Retropneumoperitoneum und Pneumomediastinum. By Prof. Dr. Umberto Cocchi. Price, $17.85. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1957.

This is a comprehensive treatise in German on the indications, techniques, and interpretation of retropneumoperitoneum and pneumomediastinum. Approximately two-thirds of the volume is devoted to retropneumoperitoneum, and the remaining one-third is devoted to pneumomediastinum. There are 142 radiographic illustrations of good quality in reverse black-and-white relationship. Many of the illustrations have accompanying explanatory line drawings. Both sections have rather complete chapters on the roentgen interpretation of the normal retropneumoperitoneum and pneumomediastinum. In addition there are chapters dealing with the anatomy pertinent to these studies. The techniques involved are fully described with excellent illustrations. There is an excellent bibliography.

HAROLD J. MATTHIES, M.D.

Roentgen Signs in Clinical Diagnosis. By Isadore Meschan, M.D. Price, $20. Pp. 1058, with many illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

The need for every clinician to be generally informed about matters relating to radiology is not always appreciated widely. Experienced clinicians, however, realize that the x-ray, like other laboratory procedures, is merely an extension of the physical examination. As such it is an essential part of the diagnostic armamentarium. Unless one works in close collaboration with an active department of radiology or an earnest radiologist who has kept up to date with modern programs, he may be unaware of many of the recent advances and much of the well-established knowledge of radiology which has enormously important bearing on general problems in internal medicine. This handsomely illustrated and well-organized book should be an extremely valuable reference for every practicing internist, for the book is detailed enough to give the necessary information without being too technical for the well-informed internist to use with profit. It would be of value if read and studied as well as being used for casual reference.

WILLIAM B. BEAN, M.D.

A Textbook of Histology. By Alexander A. Maximow and William Bloom. Seventh edition. Price, $11. Pp. 628, with 1082 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

The seventh edition of this textbook brings us up to date with many of the current advances and concepts in the field of histology. The most notable addition is the clear electron micrographs which have been added to several sections of the book. Although many chapters have not been altered much in this new edition, rather extensive revisions and additions have been made in areas covering the cell, skin, nervous tissue, and hormones. The clear and accurate presentation of the subject of histology, the excellent plates, and the adequate references to original literature make this textbook a must for medical students and a valuable asset to the physician's library.

RALPH G. JANES

The Hyphophyseal Growth Hormone, Nature and Actions. International Symposium sponsored by the Henry Ford Hospital and Edel B. Ford Institute for Medical Research. Edited by Richmond W. Smith, O. H. Gaebler, and C. H. Long. Price, $12. Pp. 576, with 270 illustrations. The Blakiston Company (Division of McGraw Hill Book Company, Inc.), 330 W. 42d St., New York 36, 1955.

The scope of the symposium was encyclopedic, providing essential information for everyone interested in the growth hormone, its character and effects. An important impression of the

symposium was that some reputable investigators were still not convinced that a true growth hormone exists. Indeed, the confusion of contradictory opinions was similar to the description given twenty years earlier by Harvey Cushing. In giving the 1921 presidential address before the Association for the Study of Internal Secretions, on "Disorders of the Pituitary Gland, Retrospective and Prophetic," he began, "We find ourselves embarked on the fog-bound and poorly charted seas of endocrinology. It is easy to lose our bearings for we have, most of us, little knowledge of seafaring and only a vague idea of our destination . . . ."

The mariner's log on the anterior pituitary "growth" hormone was brought up to date with this publication. The course of future investigation was shown as Wilhelmi presented data concerning the species specificity of growth hormone from ox, sheep, pig, horse, and frog pituitaries. This provided a tentative explanation for the failure to demonstrate growth hormone effects in man up to the time of the symposium, Oct. 27-29, 1954.

From all accounts, in terms of organization and functioning, the symposium was a utopian success. The three hundred participants represented many scientific disciplines. Most of the eminent investigators who have participated in the development of present concepts concerning growth hormone were included. Presentations were recorded as given, including the discussions. One editor was responsible for revising this material, without submitting the material to the respective speaker or discussor. This was done to expedite the publication of this material to the many readers anticipated (publication being accomplished on May 2, 1955). However, one innovation for symposia was omitted, a subject index including the valuable material presented by discussers. Such a device, although expensive and time-consuming, would have greatly added to the utility and accomplishment of this symposium.

Recent months have brought significant increases in our knowledge concerning growth hormone. C. H. Li has reported on the physical and chemical properties of bovine, monkey, and human growth hormone (*Chemical Engineering News* 34:46 [Nov. 12] 1956). Knobil, Wolf, Greep, and Wilhelmi reported the effectiveness in regard to carbohydrate and nitrogen metabolism of monkey growth hormone in hypophysectomized monkeys, where bovine growth hormone had been ineffective (*Endocrinology* 60:166-168 [Jan.] 1957). Finally, Raben, Beck, Verning, et al. (*Science* 125:883-885 [May 3] 1957) have reported the effectiveness of both monkey and human growth hormone in humans. The problem ahead is that of an adequate supply of potent growth hormone for further studies and maintenance of patients.

With our knowledge concerning growth hormone entering a new phase, this symposium provides an excellent summary and essential reference data for those interested in understanding or assessing the metabolic consequences of this hormone in man.

RICHARD E. PETERSON, M.D.

The Metabolic Response to Neonatal Surgery. By P. P. Rickham, M.S., D.C.H., F.R.C.S. Price, $5. Pp. 93. Harvard University Press, Cambridge 38, Mass., 1957.

The third, and central, chapter of this book is a new chapter in the balance study of surgical patients. Nine neonatal patients are presented in detail as regards their daily hemoglobin, hematocrit, blood urea, plasma alkaline reserve, plasma chloride, plasma sodium, plasma potassium, plasma protein, red cell nitrogen, red cell chloride, red cell sodium and potassium, weight, and eosinophil count, all of which are presented in nine tables. Bar graphs are used similar to those of Albright and Reifenstein and Moore and Ball, showing intake, output, and net gain or loss of water, nitrogen, chloride, sodium, and potassium. Single initial measurements of the distribution space of T1824, sodium thiosulphate, and N-acetyl-4-amino-antipyrine were made in four patients. Each case is presented in detail and discussed. All of this is then briefly summarized at the end of the chapter. Current and historical work on the metabolism of infants and the response of adults to surgical trauma is outlined in the introduction beginning with Boussingault's study of the metabolism of a cow, published in 1839. Standard analytical procedures were adapted to an ultramicro level, so that the day's analyses could be carried out on 1 ml. of blood, obtained by puncture of the heel of a warmed extremity.

Much related work is reviewed in a general discussion. The author is well aware that his subjects are showing response not only to surgery but to recent birth and growth. None of the infants operated on within the first few days of life lost excessive amounts of potassium. Their nitrogen and potassium loss suggested simple starvation rather than an "alarm reaction." Postoperative retention of sodium and chloride occurred, but only after the first few days. The eosinophil response was completely unpredictable and irregular during this early few weeks of extrauterine life, regardless of the severity of trauma. A final chapter, on practical applica-

tions, contains valuable advice regarding the care of neonatal patients based on the author's total experience. In this chapter the pertinent empiricism which is the mainstay of medical practice is presented, with a few minor modifications.

The book is important because of the data presented and because of the stimulus to interest in this small but important part of medical practice and not because of any startling new discoveries. The most exciting idea presented is that a neonate is peculiarly resistant to and unaffected by severe trauma of birth and surgery. An understanding of the mechanisms of this would be of great interest. Apparently the picture changes at about three weeks, when trauma brings forth a response more typical of the adult.

The author is to be congratulated on his collection and presentation of data and his conservative interpretations. The work is well organized, and many useful references are given. The research worker and clinician, surgeon, and pediatrician will all find this worth their time.

EDWARD E. MASON, M.D.

Treatment of Burns. By Curtis P. Artz, M.D., and Eric Reiss, M.D. Price, not given. Pp. 250, with 104 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

The authors have achieved their purpose of providing a useful guide for the treatment of burns. Their experience permitted them to select from the vast literature those references which effectively supplement the clinical experience of the surgical research unit of the Brooke Army Medical Center, which provided the main source material for this book. More than one thousand burn patients were seen at the Brooke Army Medical Center during the seven-year interval 1949 to 1956.

All the important aspects of the clinical problems which the burn patient presents are amply dealt with. A succinct and practical description of the pathologic physiology essential to an understanding of these clinical problems is included. The metabolic response to the burn injury is briefly and clearly presented. Fluid replacement, the initial and late care of the burn wound, infection, nutrition, hormone therapy, and technique are discussed; useful information, such as methods for preparation of intravenous fluids, feeding formulas, dressings, specific drugs and dosages, and recommendations regarding instruments, is included. Short chapters devoted to specific types of burn wounds, complications, and civilian disasters add to the value of this book.

The text is terse; the large type facilitates easy reading. A sufficient number of diagrams and photographs are effectively used to illustrate the text. Color would have improved the photographs, but not commensurate with the added cost. A more adequate treatment of the special problems presented by children and elderly burned patients would have been valuable to the clinician in civilian practice. The repetition of the subject matter which occurs is probably warranted for the benefit of those using the book as a reference. The bibliography is brief and well chosen.

An invaluable aid to any clinician responsible for the care of the burned patient, this book should be particularly attractive to the medical student, intern, resident, and practicing surgeon. The well-chosen references to current investigations in this field provide a jumping-off place for the research-minded reader. Since it is impossible for one book to be all things to all people, the reader will find minor but unimportant deficiencies. This brief book is highly recommended as an up-to-date, authoritative, eminently useful statement of the present status of the treatment of the burned patient.

JOSEPH A. BUCKWALTER, M.D.

Pain and Pleasure: A Study of Bodily Feelings. By T. S. Szasz. Price, $5.50. Pp. 301. Basic Books, Inc., 59 Fourth Ave., New York 3, 1957.

Here is one of the better statements on a vast problem so close to the core of the work of clinical medicine. It must be abundantly obvious to the busy physician that his concepts of pain are at best a temporary scaffolding on which he may orient himself, albeit unsteadily. Analgesics that don't relieve, assurances that betray, surgery that devolves into an endless chain of operations, placebos that "work" in 40% of cases, and the sometimes amazing effects of hypnosis all point to the probability that pain is beyond theoretical explanations currently popular. It is not uncommon for the harrassed physician to take refuge in a formulation that if the patient's statement does not refer to the body as he knows it, then it is nonsense. This is a handy defense, but it just isn't elegant. Now there becomes available in

Szasz' book an instrument whereby this "knowing" may be extended, and thereby both patient and physician become less frustrated by the problem of chronic pain.

Szasz, who is Professor in the Department of Psychiatry at Syracuse, examines pain (not to forget pleasure) as a multidimensional quality and not as a single sensory modality. He brings to his work not only insights developed from his medical training (he served a residency in internal medicine at the Cincinnati General Hospital) but also insights from philosophy, psycoanalysis, and sociology. Unlike so many experts who deal with a subject exclusively according to their own unique competence, Szasz, in his development of a psychology of pain and of pleasure, knows the methods of approach other than his very own. He presents a continuing case for the multidimensional outlook and appreciation of the hard work that has gone to build physical theories concerning pain.

He argues brilliantly and provocatively that a psychological theory of pain be integrated into the physician's understanding, since it is unlikely that the thoughtful doctor will be satisfied with anything less than an awareness of the relevance of the medical and the psychological processes. The book is a detailed exposition of the specific symbolic meanings of pain and pleasure which are acquired in the process of growing up; the communicative aspects of these qualities are its particular message.

It is a pleasure to have this book available. It has been a long time coming. This is a thoughtful, stimulating, and well-written book, sprinkled with the salt of Bertrand Russell, Whitehead, Goethe, and persons like them. The book is well constructed, with large type on nonreflective paper. The physician who digests and assimilates its message will no doubt extend his understanding of the process of communication to the benefit of his patient, to say nothing of himself.

CHARLES D. ARING, M.D.

News and Comment

ANNOUNCEMENTS

Course in Interpretation of Complex Arrhythmias.—A course in interpretation of complex arrhythmias will be given at Michael Reese Hospital by Louis N. Katz, M.D.; Richard Langendorf, M.D., and Alfred Pick, M.D. This is an advanced course, intended only for experienced electrocardiographers. The class will meet daily from 9 a. m. to 5 p. m., Dec. 9 to 13, 1957.

Further information and a copy of the lecture schedule may be obtained from the secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16.

Conference on Pulmonary Circulation.—The Chicago Heart Association will sponsor a conference on the pulmonary circulation, to be held Thursday, Friday, and Saturday, March 20 to 22, 1958, at the Palmer House.

Introductory sessions will be devoted to the physiology, anatomy, and pathology of the pulmonary circulation, with special emphasis on methods of clinical study. Later sessions will cover the pulmonary circulation in congenital heart disease, primary lung disease, and acquired heart disease.

Among the distinguished visitors who are accepting major responsibility in the planning and execution of the conference are Dr. Julius Comroe, University of Pennsylvania Graduate School of Medicine; Dr. Howard Burchell and Dr. Jesse Edwards, of the Mayo Clinic, Rochester, Minn.; Dr. Paul Wood, from the Institute of Cardiology, London, and Dr. Lars Werko, of Goteborgs Universitet, Gothenburg, Sweden.

It is the objective of the conference to bring together major contributors to this controversial field. Each participant will present his own recent work, and opportunity will be provided for discussion. The meeting will be open to physicians and scientists.

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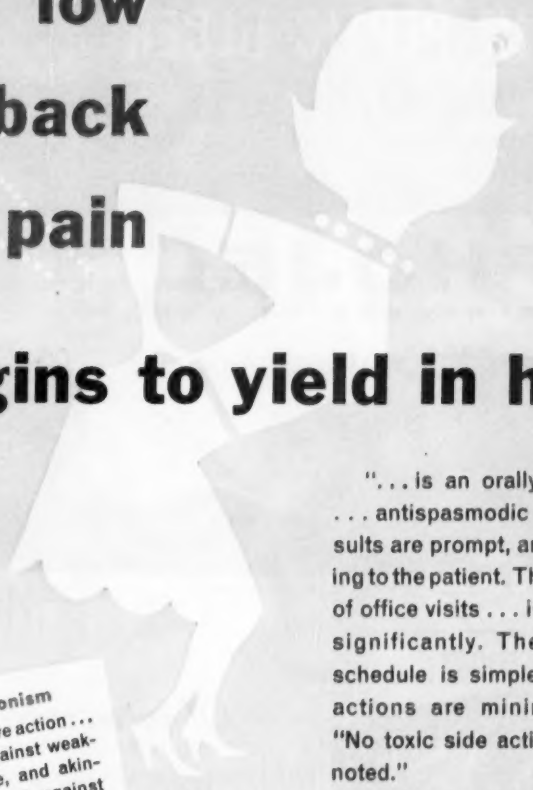

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Finch, J. W.: Orphenadrine (Disipal) in Skeletal Muscle Disorders. To be published.

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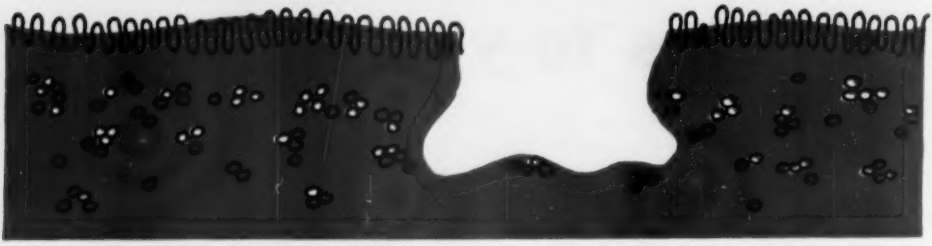

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Longmire, Wm. P., Jordan, Paul H., and Briggs, John D., Annals of Surgery, 144:4, 688, 1956

Everson, T. C., Grossman, M. I., and Ivy, A. C.: Bulletin of Amer. College of Surgeons, January, 1950.

Literature on request.

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1. Dickel, H. A., Wood, J. A. and Dixon, H. H.: Electromyographic studies on meprobamate and the working, anxious patient. Ann. New York Acad. Sc. 67:780, May 9, 1957.

2. Dickel, H. A., Dixon, H. H., Wood, J. A. and Shanklin, J. G.: Electromyographic studies on patients treated with meprobamate. West. J. Surg. 64:197, April 1956.

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[1]Fuller, H. L. and Kassel, L. E.: Antibiotic Medicine and Clinical Therapy, 3:322, October 1956.

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